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## Editorial

# THE PRESENT STATUS OF PSYCHOPHARMACOLOGY

MICHAEL SHEPHERD, M.A., D.M., D.P.M.*
LONDON, ENGLAND

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ALTHOUGH the "action, and mode of action, of drugs on mental activity in man"[1] have interested pharmacologists and psychologists since the nineteenth century and have fanned clinical activity from time to time, this complex field has remained the province of a small number of individuals until very recently. It has been suggested that the previously poor representation of the subject in the main spectrum of scientific enquiry has been due in some measure to the relative inaccessibility of phenomena which have often been more familiar to the anthropologist and the student of comparative religion than to the laboratory worker. Times have changed: psychopharmacology, which Macht referred to as "virgin soil, full of possibilities" as early as 1920, has received full recognition in the past decade. The term is now widely employed to cover a large group of diverse activities and has been sanctioned by at least one major textbook of pharmacology; the new developments have been propagated by several volumes, a torrent of articles, an international society, and a new journal.

The background of this resurgence of interest in psychopharmacology deserves closer attention than it has received. Without question it has been linked chronologically to a wave of therapeutic expansion in the sphere of mental illness. Since the early 1950's substantial claims have been made for the phenothiazine derivatives, the Rauwolfia alkaloids, and their many successors in the treatment of a variety of psychiatric disorders. Had one tithe of these claims been substantiated, the results in themselves might have been taken to justify the tumult and the shouting. A closer scrutiny quickly disposes of this specious explanation

*Reader in Psychiatry, Institute of Psychiatry, London, England.

for it has proved excessively difficult to establish convincing evidence of the therapeutic efficacy of the newer compounds. Many attempts have been made to apply the techniques of the modern clinical trial for the purpose, often with a higher degree of statistical sophistication than is encountered customarily in other branches of medicine. Unfortunately, the principles of the group trial have tended to founder on the rocks of diagnostic heterogeneity. Further, the range of individual drug responses has proved to be so great as to have stimulated a growing appreciation that most discrepant reports on the clinical efficacy of the new drugs reflect not so much differences of observation as the so-called "nonspecific" action of the drug in question: apart from the rediscovery of the placebo response, attention is being paid accordingly to the influence on drug response of the subject's personality, the doctor-patient interaction, and the social milieu in which treatment is conducted.[12] Such factors are now recognized to have played a major role even in institutions where the mass effects of therapy can be observed most accurately; they have prompted one thoughtful British observer to express the opinion that ". . . if we had to choose between abandoning the use of all the new psychotropic drugs and abandoning the Industrial Resettlement Units and other social facilities available to us, there would be no hesitation about the choice: the drugs would go."[7]

It is probable that greater progress would have been made toward the evaluation of these substances if the data which have been amassed about their biologic properties had yielded more precise information about their sites and modes of action. Some of the data, however, have contributed to the analysis of function of the central nervous system and there has been complementary study of dysfunction as the necessary condition for mental disorder.[10] Probably the outstanding investigations in this area have been concerned with the biologically active amines; some of these substances, it has been suggested, may be vital to both nerve function and metabolism of mediator substances, and may also be implicated in the mechanism of drug action.[2] 5-Hydroxytryptamine, for example, meets some of the requirements for a transmitter substance; it also appears to be released from its storage sites in the body under the influence of reserpine, and its inactivation by amine oxidase has led to several exercises in chemotherapeutic logic on the mode of action of the supposedly antidepressant drugs which inhibit this enzyme.[3] At the same time it must be emphasized that in this instance, as in all the others which have been examined so far, the efforts which have been made to explain clinical responses in terms of a biochemical "lesion" have proved disappointing.[5]

Another group of studies has concentrated on the properties and implications of those drugs which simulate psychosis-like states resembling the schizophrenias. The investigations represent the most recent labors of a long chain of workers who have always been stimulated by the hope that an understanding of the induction of psychotic symptoms might lead to an understanding of the means to dispel them.[9] The discovery of lysergic acid diethylamide led to a burst of activity in this field but it is now realized that the differences between the artificially induced reactions and the disease process are at least as great as the similarities.[15] A third approach has been directed to a consideration of what have

been regarded as the side effects of neuroleptic drugs in relation to their therapeutic action.[4] There is as yet little evidence to confirm or refute the suggestion that these phenomena are closely associated.

The gap between biologic properties and clinical effects has directed the attention of many pharmacologists to the long line of investigations by experimental psychologists which reach back to Wundt's early work. These studies have flowered into an intensive examination of the behavioral effects of centrally acting drugs by means of a series of ingenious techniques which have been developed to ensure that quantitative data may be obtained about such reactions as motor response, discriminating function, and learning, as well as about various emotional states.[16,17] While a great deal of knowledge has accrued about the behavior of such organisms as the hungry pigeon, the thirsty rat, and the frightened monkey, relatively few attempts have been made to determine whether the information can be applied to human responses.[13] Evarts[6] has suggested that the gap be bridged by the choice of a particular psychological abnormality in a particular type of psychiatric illness, e.g., the disturbance of association in schizophrenia, which could be examined by the development of animal tests designed to assess this disturbance or its analogue. The inverse process has been adopted by the author and his colleagues who have borrowed Weiskrantz's concept of behavioral nonreactivity which was developed on the basis of animal experiment[14]; it has proved possible with human subjects to test the hypothesis that the poverty of response following the administration of reserpine is related primarily to the blockade of sensory stimuli rather than to disturbance of motor or associational function.[11]

In the light of current knowledge it would be difficult therefore to base the reputation of psychopharmacology on a large body of established knowledge about either the therapeutic value or the pharmacodynamic action of the psychotropic drugs. To what then can the high status of the subject be attributed? Though it may not be possible yet to provide a comprehensive answer to this question it is apparent that a full explanation does not fall within the framework of the physical or clinical sciences. Status, we may recall, is a sociologic concept closely related to economic class, and the evidence supports Professor Toman's view that it has been the socioeconomic impact of new drugs in psychiatry which has inspired the "veritable explosion of research on the action of drugs." For 150 years the history of the therapeutics of mental disorder has demonstrated the importance of social and professional attitudes as the pendulum has oscillated between the "moral" and the so-called physical methods of treatment. In retrospect it is clear that the newer pharmacologic compounds were introduced to psychiatry at a time which favored their adoption: on the one hand, a growing disillusion with psychological treatment had become increasingly evident even where these methods had been taken up with most enthusiasm; on the other, the seams of the older physical methods of treatment had been exhausted and even their most ardent advocates were dissatisfied with the crudity of the empirical tools at their disposal. The great majority of eclectic psychiatrists had long recognized the limitations of available methods of treatment and they have welcomed the clinical possibilities of the new drugs, finding great advantages

in the relative flexibility of pharmacotherapy and, less obviously, in the employment of measures which are more in keeping with the traditional forms of medical care. Their eagerness to employ pharmacologic methods of treatment, stimulated by a vigorous campaign on the part of the pharmaceutical industry, has played an important role in the widespread adoption of drug therapy in psychiatric institutions. The still more extensive use of drugs in the extramural practice of psychiatrists and general practitioners appears to reflect not only the attitudes and habits of physicians but also the expectations of their patients as representatives of a public alive to the importance of mental distress and strongly influenced by the cult of tranquillity. In his elegant study of the social aspects of prescribing, Martin had indicated how what he calls "custom" can be at least as potent as the therapeutic value of the drugs themselves in determining the choice of medication.[8]

Nonetheless, while the rise of psychopharmacology carries lessons for the medical sociologist, an interdisciplinary scientific program of great potential value has been evolved. Whatever the practical outcome of the effort which is being expended on the pharmacotherapy of neuropsychiatric disorders, it is certain that the interest of distinguished workers in many fields has been aroused and encouraged by the preliminary findings. Their work signifies aspiration rather than achievement at the present time, but the assurance of their prospective collaboration justifies a sober optimism for the future.

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# AN EXPERIMENTAL STUDY OF COMPARATIVE RESPONSES OF BLOOD PRESSURE TO DIFFERENT NOXIOUS STIMULI

ALVIN P. SHAPIRO, M.D.*
PITTSBURGH, PA.

*From the Department of Clinical Science, School of Medicine, University of Pittsburgh*

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PSYCHOPHYSIOLOGIC responses of the blood pressure have been studied extensively and it appears to be well established that lability in the hypertensive patient is determined in large measure by emotional stimuli. Moreover, that emotional disturbances may aggravate hypertension and its pathologic concomitants, and that their alleviation is often associated with a decrease in blood pressure, seems probable from available data.[1,2] How these facts fit in the over-all pathogenesis of hypertensive disease is by no means clear, however. When we attempt to determine what specific types of emotional conflict result in blood pressure elevation, to correlate the intensity of conflict with the degree of pressor response, and to decide if different emotional reactions produce different patterns of blood pressure response, we find a notable lack of quantitative data. Accordingly, this study in a group of hypertensive patients was designed with the following questions in mind: (1) Is the magnitude of the blood pressure response to a "psychological" stimulus in a hypertensive patient equivalent to that which follows a "physical" stimulus? (2) What role do factors such as age, sex, hypotensive medication, and initial levels of blood pressure play in determining responsiveness in the hypertensive patient? (3) Assuming that systolic elevation indicates primarily an increase in cardiac output and diastolic elevation an increase in peripheral resistance, does the pattern of response to different stimuli vary? Although similar studies have been reported, it was hoped that with the use of careful statistical design and analysis, along with a new method of measuring blood pressure, more precise quantitative data could be obtained.

In addition to hypertensive patients, a small group of normotensive individuals, with and without a family history of hypertension, were studied similarly.

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*Present address: Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

METHODS AND MATERIALS

A recently developed indirect blood pressure recorder* was utilized in our investigations.[3] This device permits repeated determinations of both systolic and diastolic blood pressures, automatically, every 1½ minutes for long periods of time, with minimum discomfort to the patient and without the attendance of the investigator. In addition to convenience, its use offered several other advantages over the manual cuff method. Since the patient can be left unattended, the difficulties in achieving a base line created by the continual presence of the investigator at the bedside were obviated. That the mere presence of the investigator in the room had a definite effect on blood pressure was suspected and was borne out empirically by data which will be presented. Second, when auscultation is performed by the investigator, factors such as fatigue, inattention, and unconscious bias undoubtedly operate to influence his readings; these problems are absent in a machine and hence greater objectivity is possible. Blood pressures determined simultaneously with the automatic recorder and with the usual manual indirect technique were not significantly different, while slight differences from values obtained with direct interarterial readings were not relevant to this study which dealt with relative changes in individual subjects.

Pulse rate was recorded by a cardiotachometer† operating from a photoelectric pickup attached to the ear lobe. Its operation was synchronized with the blood pressure recorder so that for each cycle of blood pressure measurement, lasting 20 to 30 seconds, a pulse rate curve was inscribed. The rate per minute at the time of the blood pressure measurement was calculated from this curve by averaging its highest and lowest points. Since the cardiotachometer was not obtained until midway during our studies, pulse rate measurements are available only for approximately half of the hypertensive patients, but for most of the normotensive subjects.

In designing the noxious stimuli, it was recognized that no stimulus, no matter what its intent or how constant its manipulative technique, could be considered to be equally meaningful and intense to different patients. Therefore, in the present study, instead of seeking to determine precisely the "meaning of the stimulus," we attempted rather to minimize variations statistically by the following: (1) Stimuli were conceptually simple, and operationally could be easily duplicated. (2) Tests were done by a single investigator and under identical environmental and laboratory conditions. (3) A comparatively large sample of subjects was studied. (4) In the hope of randomizing any bias stemming from the doctor-patient relationship, subjects were selected from several sources (ward, clinic, and private) and individuals were included with variations in frequency and intensity of previous contacts with the investigator.

At the conclusion of the blood pressure studies, a simple self-administered psychological test was given to the majority of the subjects. This test, devised by Dr. Dean Clyde of the Psychopharmacology Service Center, National

*Automatic blood pressure recorder, Model 110, Gilford Instruments Laboratories, Inc., Oberlin, Ohio.

†Digital cardiotachometer, Model 120, Gilford Instruments Laboratories, Inc., Oberlin, Ohio.

Institutes of Health, and referred to as a "Mood Scale," is based on an adjective check list and consists of 133 cards on each of which is printed a single adjective or adverb descriptive of affect. The subject sorts each of the cards into one of four categories, ranging from "not at all" to "extremely," in order to describe how he "feels today." In the present study, the subject sorted two stacks of cards, one to describe himself and the other to describe how he "thought the investigator felt today." Clyde has set up a scoring system based on a simple weighting scheme which gives a numerical value for six factors described by the following adjectives: friendly, energetic, clear-thinking, aggressive, jittery, depressed. These factors show some degree of intercorrelation but in the psychopharmacologic studies for which the scale was originally devised appeared to be differentially useful in describing psychiatric conditions. The raw scores are converted to a "standard score" which is based on a mean of 50 with a standard deviation of 10 for a sample of 200 "normal" subjects. Thus, the deviation of a subject's score from a standard score of 50 supplies an approximate frame of reference. In addition, as used in our study, the difference between the standard scores on self- and investigator ratings was considered an estimate of the attitude of the subject toward the investigator on the day of testing.

The actual protocol of the experimental session and the descriptions of the stimuli employed follow. After attachment of the apparatus, the subject was allowed to rest, alone, in a quite and pleasant room, for 15 to 30 minutes, while blood pressure and pulse measurements were recorded automatically at 1½ minute intervals. The following test stimuli then were administered, with periods of 15 to 30 minutes of rest between them:

*Test 1.*—Investigator entered the room, informed the subject he would receive an injection, and filled a 10 ml. syringe with normal saline (1); prepared the patient's arm for venipuncture (2); performed the venipuncture (3); and gave the injection while having the patient count aloud slowly from 1 to 100 "to control the rate of administration" (4). All other comment was avoided. The four steps were done slowly and methodically, and were timed so that a blood pressure reading was recorded at each step. The maximum systolic and diastolic elevations and the rise in pulse rate, as compared with the average of the four determinations immediately prior to the entry of the investigator, were calculated. This stimulus might be considered as one evoking "fear."

*Test 2.*—The investigator entered the room and informed the subject that he had moved and "spoiled the previous test" and that the injection would have to be repeated. This was done as before except that the subject was told to "count backward from 100 as rapidly as possible" during the injection, and the investigator continually prodded the subject for speed and accuracy. This stimulus might be interpreted as evoking anger but, although subjects frequently voiced the claim that they had not moved, rarely was any more outspoken objection raised.

*Test 3.*—The investigator entered the room and performed a cold pressor test, measuring the blood pressure one minute after immersion of the hand in crushed ice.

*Test 4.*—The investigator entered the room and, after an explanation, had the subject read from a chart on which a series of names of colors was printed in colors other than the name itself (e.g., the word "red" was printed in green, "green" in yellow, etc.). The subject was asked to "read the color, not the word"; speed and accuracy were demanded and several negative comments on the subject's performance were made by the investigator during the performance. The "color reading" was continued from the end of one cycle of blood pressure recording to the beginning of the next, a period of approximately 1½ minutes. Subjects' complaints regarding this test ranged from objections to its unfairness to excuses for their inadequacies in its performance. Others have considered this test an exercise in ability to "hold two thoughts in consciousness at one time."[4] As used here, however, it appeared to serve as a frustrating task.

The Mood Scale was administered after all tests were completed and the patient detached from the apparatus.

Fifty hypertensive patients, 25 men and 25 women, were studied. Selection of subjects was essentially consecutive, based on clinic visits or hospitalization during the period of the study, with adjustments to achieve an equal sample of both sexes. Patients receiving specific hypotensive drugs were included. All patients had blood pressure levels of at least 150/90 mm. Hg when selected; a few, however, showed lower base-line pressures at the time of the testing procedures. Table I indicates the various measures of severity in the group.

A sample of normotensive patients also was studied both to analyze responses in a control population and to undertake a pilot study of differences in response between healthy subjects with and without a family history of hypertensive vascular disease. This sample consisted of 18 patients with various types of neurotic and psychopathic disorders from the inpatient service of the Western Psychiatric Institute, and 18 medical students who were "paid volunteers." Of the entire group of 36 subjects without hypertension, 14 had a family history of hypertension in at least a parent, grandparent, or sibling. The same protocol was followed as for the patients with hypertension, except that, since preliminary analyses had indicated no significant differences in the responses to Tests 1 and 2, only the former was administered. Accordingly, the order of administration of the three remaining tests was randomized.

## RESULTS

*Responses to the Four Tests in Hypertensive Patients.*—Fig. 1 indicates the actual tape of the response of one patient to Tests 1 and 2. Fig. 2 depicts the average responses of all 50 patients to the four steps of each of these two tests. The progressive nature of the blood pressure response to the saline injections along with the effect of entry into the room by the investigator is thus illustrated. Fig. 3 presents the mean responses of the 50 hypertensive patients to each of the four noxious stimuli. The first injection of saline (Test 1) resulted in a mean change of 31/13 mm. Hg, while the repeat saline injection (Test 2) produced a response of 27/13. The response to the cold pressor test (Test 3) was 36/27 mm. Hg while that to the "color reading" test (Test 4) was 21/6. Analysis of variance revealed the differences to be highly significant ($F = 7.37$ for systolic changes and 55.4 for diastolic changes; $p < .001$ for both). Comparison of p values for the various individual means indicated that the responses to the two saline injections did not differ significantly, but both the systolic and diastolic response to the first saline injection and the diastolic response to the repeat injection of saline were greater than the equivalent responses to "color reading" (Test 4) ($p = .01$ to $.001$). The diastolic response to all three "emotional stimuli" was significantly less than that to the cold pressor test ($p = .001$). However, the systolic response to the first saline injection was not less than that to cold, although the systolic responses to Tests 2 and 4 were less ($p = .01$ and $.001$, respectively). In keeping with the differences in patterns of blood pressure response, the systolic/diastolic ratio was highest for Test 4 (3.2) and lowest for Test 3

(1.4), suggesting that the latter test exerted the most marked effect on peripheral resistance.

The pulse rates of 26 patients were measured and showed increases of 8, 12, 12, and 11 per minute on the four tests, respectively. These changes were not significantly different ($F = 1.53$; $p > .05$).

The pretest blood pressure readings for the four tests ranged from 172/104 for Test 1 to 183/107 for Test 4, and analysis of variance demonstrated that they were not significantly different ($F = 1.47$, $p > .05$ for systolic and $F = 1.28$, $p > .05$ for diastolic).

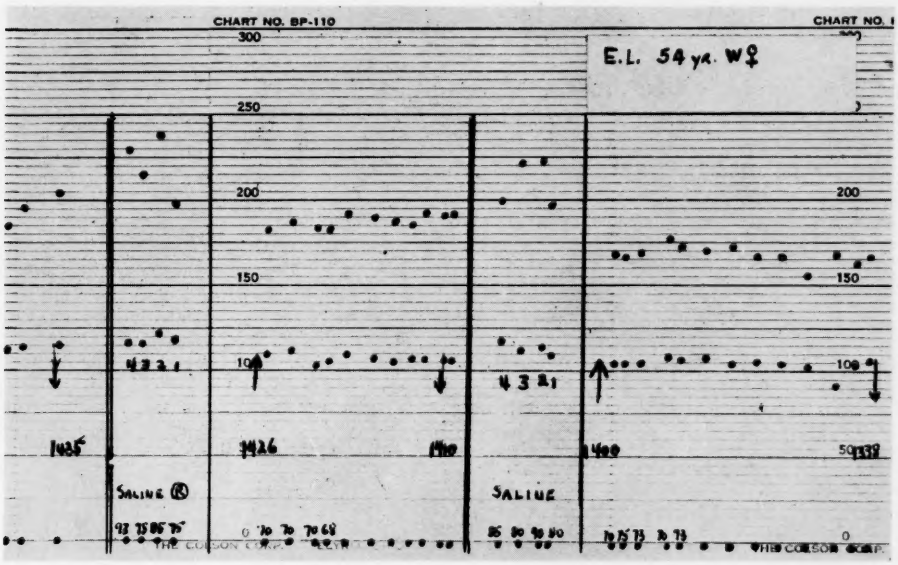


Fig. 1.—Actual tape from automatic blood pressure recorder of response of a 54-year-old woman to saline injection (Test 1) and repeat saline injection (Test 2). Record moves from right to left; for each consecutive pair of dots, the upper one represents systolic, and the lower diastolic blood pressure, respectively. At the arrow marked *1338*, the investigator left the room, returning 22 minutes later at *1400* to inject saline. The numbers *1, 2, 3, 4* refer to the steps of this injection as outlined in the text. The figures along the base line represent the pulse rate per minute recorded on a cardiotachometer simultaneously with the corresponding blood pressure measurement. The repeat saline injection was performed at *1426*.

The lack of a relationship between the pretest blood pressures and the responses to the various tests is illustrated further in Fig. 4. A questionably significant positive correlation between the systolic response to saline and the pretest systolic blood pressure ($r = .283$; $p = .05$) was the only finding of note. Fig. 4 also indicates the spread of responses among the subjects in Tests 1 and 3, which is representative of the variability in each of the four tests.

*Relationship of Sex and Age to Responses.*—Comparison of the mean responses to first saline injection (Test 1), cold pressor (Test 3), and "color reading" (Test 4), between men and women and between patients over and under age 51 is presented in Fig. 5. (To simplify analyses, the response to the repeat saline

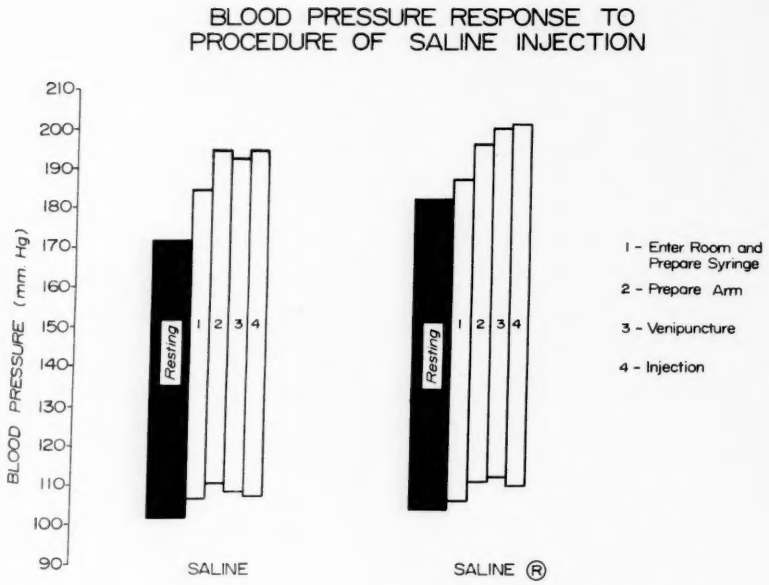


Fig. 2.—Average response of 50 hypertensive patients to each of the four steps of the saline injection (Test 1) and repeat saline injection (Test 2). Resting pressure (wide black bar) represents average of entire group for the four readings immediately prior to the tests.

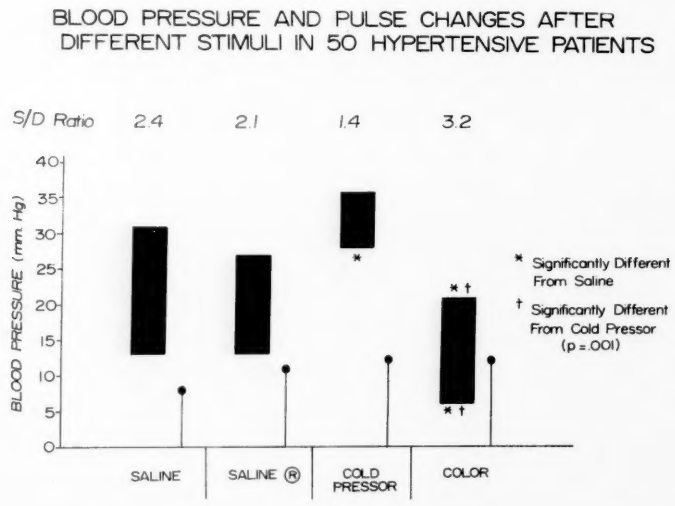


Fig. 3.—Average responses to 4 different noxious stimuli in 50 hypertensive patients. The upper border of each black bar represents the rise in systolic pressure; its lower edge, the rise in diastolic. The lines with black circles indicate the average pulse rate increase. The differences between the response to saline-R (Test 2) and the remaining tests follow the same pattern of statistical significance as those indicated for saline (Test 1) in the figure, with the additional finding that the systolic response to saline-R is significantly lower than that to cold pressor ($p = .01$), whereas this is not the case for Test 1. (See text.)

injection—Test 2—has been omitted from this and subsequent comparisons since it was identical statistically with the response to Test 1).

The women showed blood pressure elevations of 37/13, 36/27, and 26/5 mm. Hg to Tests 1, 3, and 4, respectively; the responses of the men were respectively 24/12, 37/27, and 15/7 mm. Hg. Analysis by the "t" test revealed that the women demonstrated significantly greater systolic elevations for Test 1 ($p = .01$), and Test 3 ($p = .02$). The diastolic responses were not different. Accordingly, the systolic /diastolic ratios in women were greater than those in the men. Pulse rate data were available for 14 women and 12 men; increases of 11, 14, and 15 per minute were noted for women in Tests 1, 3, and 4, respectively; and 6, 11, and 9 per minute for the men. Again the differences between the responses of the men and women to Tests 1 and 3 were significant ($p = .01$ and .05, respectively).

A slightly more intense pressor response was obtained in the older patients, but only the diastolic responses to Test 3 were significantly different ($p = .01$), with the older patients showing a greater change.

The 34 patients who were not receiving therapy were then divided into four groups on the basis of *both* sex and age as indicated in Fig. 6. Analysis of variance for the three tests and four subgroups revealed statistically significant differences at the 0.1 to 1 per cent level related to both tests and subgroups for systolic responses, and to tests only, for diastolic responses. (Differences between subgroups in regard to diastolic responses were at the 10 per cent level). Significant interaction between tests and subgroups was absent. For systolic responses, individual differences ranging from 15.2 to 17.2 were significant at the 5 per cent level between both tests and subgroups; for diastolic responses, differences of 8.3 to 9.4 were similarly meaningful, but only between tests.

These data suggest the following interpretations: (1) Between subgroups, there is a gradient of response, primarily in systolic blood pressure, which is related to sex and to a lesser extent to age. Thus younger males are least responsive and older females most responsive. (2) The systolic/diastolic ratios of the responses to emotional stimuli in young men are consistently under 2.0, thus more closely resembling the cold pressor response than do the responses to emotional stimuli in other subgroups. (3) Within specific subgroups, the differences between the responses to the three different noxious stimuli follow the same pattern as has been described (Fig. 3) for the entire group of hypertensive patients.

*Relationship of hypotensive therapy to response.*—The 16 patients who were receiving hypotensive agents at the time of testing included 5 patients on mecamylamine, chlorothiazide, and reserpine; 4 on reserpine with chlorothiazide; 5 on reserpine alone; and 2 on chlorothiazide alone. Hypertensive disease was somewhat more severe in these 16 patients as indicated by the data in Table I. Furthermore, despite therapy, pretest blood pressures were actually higher than in the 34 untreated patients, although in only one instance was this a significant difference (Table II, Initial Blood Pressure, Test 1). As indicated in Table II, responses to Tests 1, 3, and 4 were essentially the same irrespective of drug therapy. Indeed, the systolic response to the cold pressor (Test 3) actually was

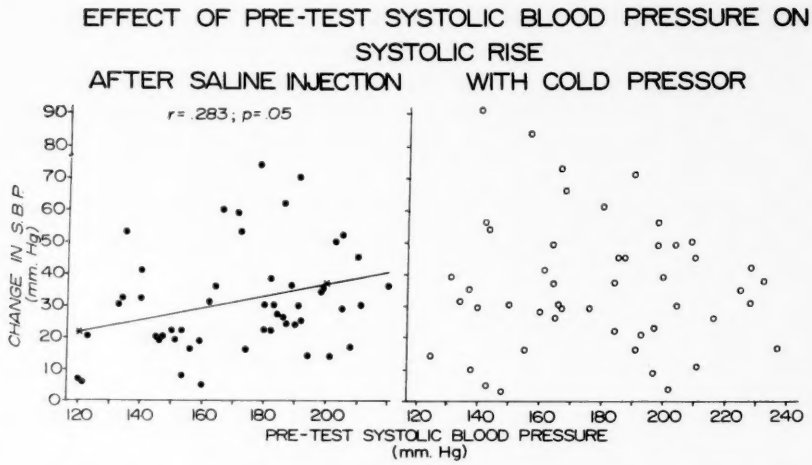
EFFECT OF PRE-TEST SYSTOLIC BLOOD PRESSURE ON SYSTOLIC RISE
AFTER SALINE INJECTION
WITH COLD PRESSOR
r = .283; p = .05
CHANGE IN S.B.P. (mm. Hg)
PRE-TEST SYSTOLIC BLOOD PRESSURE (mm. Hg)

Fig. 4A.—Relationship of response of systolic pressure to pretest systolic pressure in Tests 1 and 3. Note weak correlation in Test 1.

significantly greater (p = .02) in the treated group and approached statistical significance (p = .1 to .05) in several other instances. Thus drug therapy was not associated with a significant diminution in responsiveness.

*Pressor and Pulse Responses of Normotensive Subjects.*—Of the 36 normotensive subjects, 14 had a family history of hypertension, and 22 were without such a family history. All but 3 subjects were less than 35 years of age; these 3 were under age 51. Only 6 were women, among whom there was only one with a positive family history. Thus, age and sex, shown to be factors influencing pressor response within the hypertensive group, could not be considered important in the differences between normotensive groups described below.

The data concerning blood pressure and pulse responses were treated by analysis of variance for the three tests and two groups. The contrast between the two family history groups is indicated in Fig. 7. Subjects with a family history of hypertension had blood pressure elevations of 20/11, 22/24, and 16/7 mm. Hg on Tests 1, 3, and 4, respectively; subjects without such a family history had 12/10, 15/19, and 9/5 mm. Hg. For systolic responses, the difference between groups was significant at the 0.1 per cent level and this applied to all three tests. Diastolic responses between the two groups were not significantly different. Within each group significant differences between tests also were present, and these were of the same pattern noted between tests in hypertensive patients.

The heart rate in the group with a positive family history of hypertensive disease showed a greater increase following all three tests (21, 9, 12 per minute versus 10, 6, 8). The differences, however, were significant (p = .001) only for Test 1.

Pretest blood pressure levels in the group with a positive family history were 115/68, 116/67, and 116/71 mm. Hg for Tests 1, 3, and 4, respectively; for the negative family history group they were 105/65, 105/66, 105/66 mm.

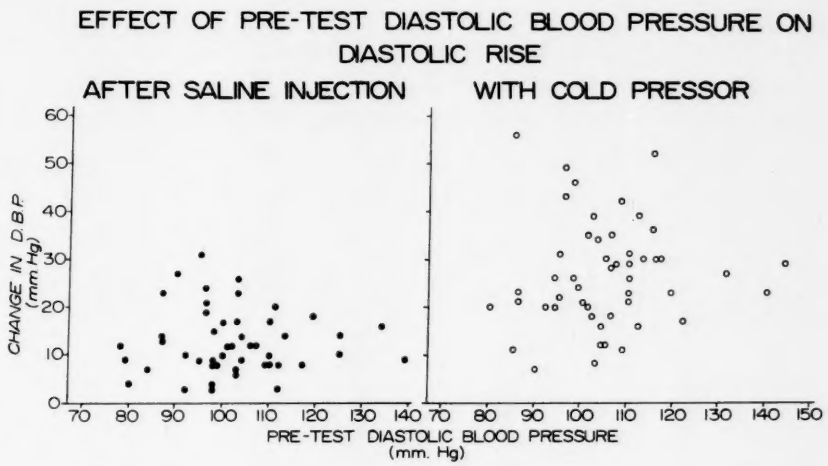


Fig. 4*B*.—Relationship of response of diastolic pressure to pretest diastolic pressure in Tests 1 and 3. No correlations are present.

Hg. The systolic levels in the positive family history group were significantly higher ($p = .001$), but the diastolic levels were identical ($p > .05$). Pretest pulse rates were 77, 74, and 73 per minute, in contrast to 72, 74, and 73 per minute ($p > .05$). The greater elevation of systolic pressure after stimulation in the group with a positive family history thus occurred despite the fact that they started at a higher initial level. This observation and the similar finding in the hypertensive group that low pretest levels did not correlate with greater pressure responses (Fig. 4) suggest that blood pressure reactivity is not significantly related to initial values, which contrasts with the demonstration by Bridger and Reiser[5] of an inverse relationship between heart rate responsiveness and basal levels. Wilder[6] has referred to the latter phenomenon as the "law of initial values," implying that it is in some sense a distinct biologic phenomenon. In point of fact, however, the effect of initial values may be fundamentally a problem of regression, related to the tendency of individuals at either extreme of a population to return toward the mean of that population.[7]

Since the 36 normotensive subjects were from two separate sources, the pressor responses in the 18 psychiatric patients and in the 18 medical students were compared. The former group had elevations of 14/9, 18/20, and 14/5 mm. Hg for Tests 1, 3, and 4, respectively; the latter, the medical students, responded with changes of 17/12, 18/22, and 9/6 mm. Hg. The means between groups were not significantly different ($p > .05$).

*Comparison of Scores on Clyde Mood Scale.*—The self-ratings and the differences between self and investigator ratings for the hypertensive group and for the normotensive individuals with and without a family history of hypertension were subjected to analysis of variance and results are indicated in Table III (Groups by B. P. Reaction). Except for a questionable increase in the self-rating "jittery" score in normotensive persons without a family history of hypertension as compared with normotensives with such a family history, significant

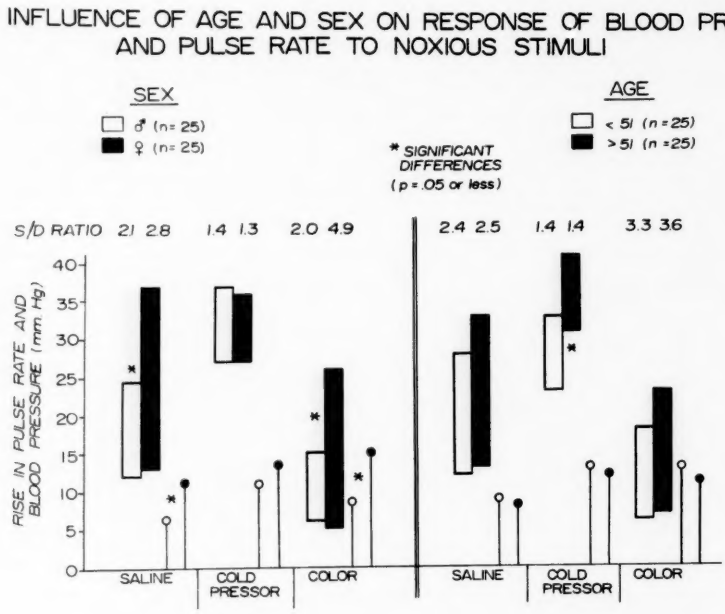


Fig. 5.—Responses of all patients, classified by sex *or* by age, to Tests 1, 3, and 4. Bars represent average blood pressure changes; lines with circles, pulse rate changes, as in Fig. 3. Shorter bars coincide with smaller systolic/diastolic ratios, and suggest proportionately greater increases in peripheral resistance.

differences were absent despite the fact that pressor responses were different between the normotensive groups. On the other hand, highly significant differences were evident (Table III, Groups by Status) in the investigator-subject interaction, and in the "clear-thinking" category in self-rating, when the normotensive subjects were divided according to whether they were patients or medical student "volunteers," although between these two categories differences in pressor responses were absent. It was of interest that the psychiatric patient subjects shared similar opinions of the investigator with the hypertensive patients, while the medical student subjects differed (e.g., hypertensive and psychiatric patients rated the investigator higher in the "friendly" score, while medical students rated him lower). In respect to "clear thinking" the psychiatric patients rated themselves lower and the doctor higher than either students or hypertensive patients.

The Clyde Mood Scale scores for men and women in the hypertensive group were compared, as well as the scores for hypertensive individuals above and below age 51. As indicated previously, differences in pressor responses were present between these categories, but no differences in Mood Scale scores were observed.

Although differences in mood scores between groups with different pressor responses were absent, a positive correlation ($p = .01$) between systolic response to saline (Test 1) and the "jittery" score was present *within* the hypertensive

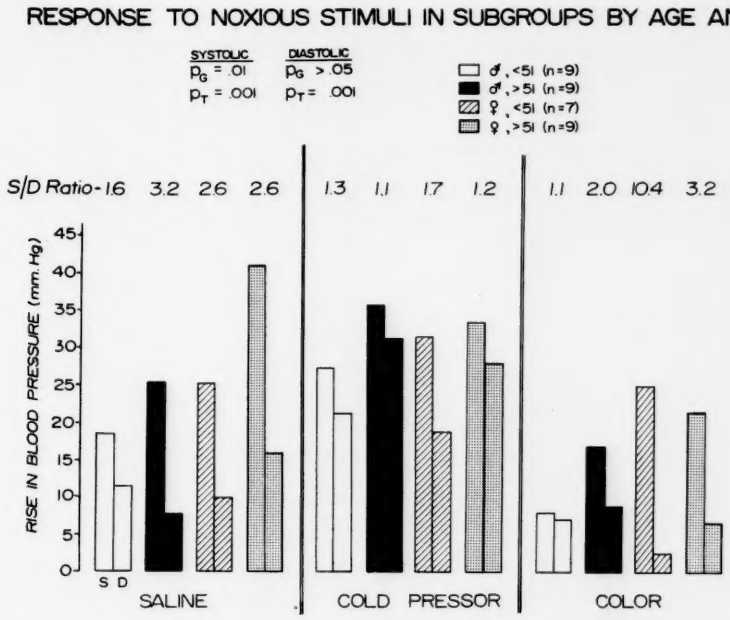


**Fig. 6.—Average responses for four subgroups, classified according to *both* age and sex, to Tests 1, 3, and 4. Systolic and diastolic blood pressure changes are expressed by individual bars, rather than by the composite "pulse-pressure" bars used in Figs. 3 and 5.**

group (Fig. 8). A similar but less marked correlation (r = .468; p = .01) was noted between this same response and the "depressed" score. No significant correlations between these two scores and systolic responses to cold pressor or to color were noted. Correlations of blood presssure response to saline and "jittery" and "depressed" scores were absent in the normotensive subjects, both within the group as a whole and within each of the two subgroups classified by family history.

## DISCUSSION

The data indicate that pressor responses to different noxious stimuli in a group of hypertensive subjects differ significantly in both intensity and pattern of reaction. Thus, although the elevation of systolic blood pressure to the cold pressor stimulus was not significantly greater than that following the "emotional stimulus" of an intravenous injection of saline, there was a greater response of the diastolic blood pressure. This implies that the cold pressor test produced a more pronounced effect on peripheral resistance. When responses to two different emotional stimuli were compared, e.g., venipuncture and a frustrating verbal task, the response of both systolic and diastolic pressures to the former was more marked. In contrast, venipuncture alone and a second venipuncture during which an attempt was made to anger the patient evoked identical blood pressure changes. Since the order of administration of the different tests was not randomized in the hypertensive group, it might be expected that the carry-over from

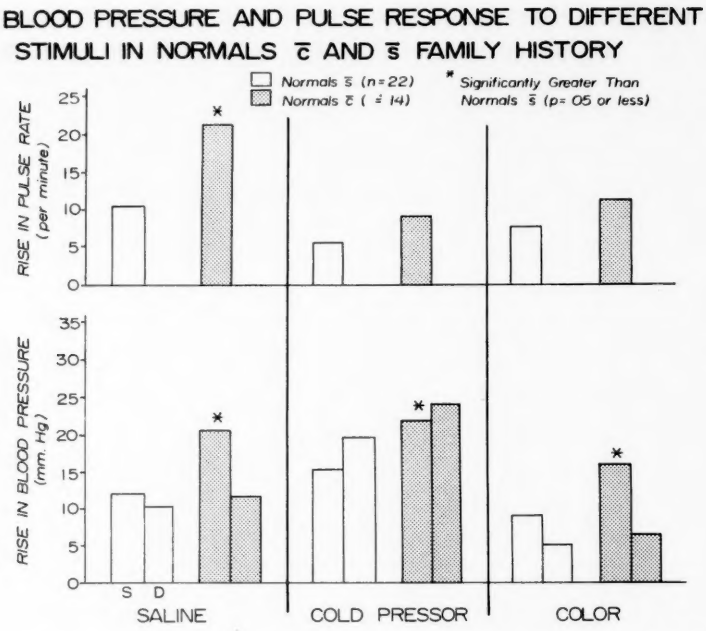
BLOOD PRESSURE AND PULSE RESPONSE TO DIFFERENT STIMULI IN NORMALS c̄ AND s̄ FAMILY HISTORY
Normals s̄ (n=22)
Normals c̄ ( = 14)
* Significantly Greater Than Normals s̄ (p= 05 or less)
RISE IN PULSE RATE (per minute)
RISE IN BLOOD PRESSURE (mm. Hg)
S D
SALINE
COLD PRESSOR
COLOR

Fig. 7.—Comparison of average blood pressure and pulse responses to Tests 1, 3, and 4 in normotensive individuals with and without family history of hypertensive disease. The individual systolic and diastolic bars, as in Fig. 6, are again used here.

earlier tests influenced responses to later tests. However, in view of the facts that an interval of 15 to 30 minutes was maintained between tests, that during this time blood pressure levels consistently returned to or near basal levels, and that differences between tests in the normotensive groups, in whom order of administration was randomized, were of the same pattern as in the hypertensive subjects, this possibility appears unlikely.

It seems evident that the emotional stimuli evoked a less profound effect on peripheral resistance than did the essentially physical stimulus of the cold pressor test. On the other hand, no explanation is available to account for the variations in intensity of response to certain of the emotional stimuli and the similarity in response to others. It would be rather a meaningless oversimplification to state that fear (Test 1) was equal in effect to fear plus anger (Test 2) and that both were more stressful than frustration (Test 4), even if it could be established that the affective responses described were actually those elicited. In fact, the most impressive feature of these tests was the relatively mild nature of the emotional stimuli and the rather profound pressor responses which resulted. Indeed, through the use of the automatic recorder, it was demonstrated that the mere presence of the investigator in the room could initiate a pressor response (Fig. 2). This suggests, as Innes, Millar, and Valentine[8] have proposed, that an "alerting response" of a rather nonspecific nature occurs in these circumstances. Since the pressor responses to emotional stimuli were predominantly

systolic in pattern, stimulation of cardiac output rather than increase in peripheral resistance is indicated as the physiologic mechanism responsible for this "alerting response." Epinephrine which predominantly has cardiac effects might be involved in such a nonspecific mechanism, without any implications as to its preferential elaboration in different types of stress.

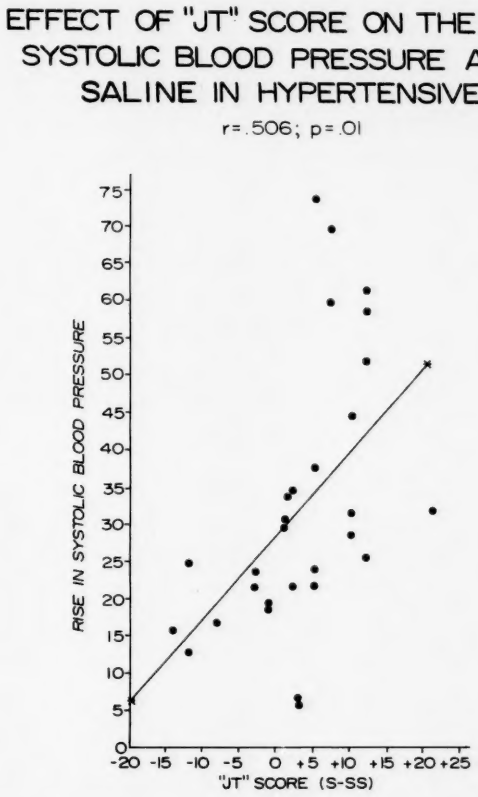


**Fig. 8.—Relationship between "jittery" scores on self-rating by hypertensive subjects and their systolic response to saline injection (Test 1). Scores are represented on the abscissa as the difference between self-rating and the standard score of 50.**

Certain characteristics of the patient appeared to affect responsiveness. Thus, among individual patients, there was considerable variation in reactivity to emotional stimuli. A few subjects tended to show a predominantly diastolic response to all four stimuli and, when the group of 50 was broken down into various age and sex categories, the younger male subjects illustrated this phenomenon most clearly. Women had more marked systolic responses than men following the emotional stimuli, but responded identically to men following the cold pressor test. The greater systolic response of women to venipuncture and to the color reading task was associated with a significantly greater increase in pulse rate, which further suggests that this difference results from a greater effect on cardiac output.

TABLE I. CHARACTERISTICS OF GROUP OF 50 HYPERTENSIVE SUBJECTS

| | NO. OF PATIENTS | AVERAGE AGE | FUNDI | | | NO. WITH CARDIAC HYPERTROPHY | AVERAGE BLOOD UREA NITROGEN (MG. %) | NO. ON THERAPY | "S.I."* |
|---|---|---|---|---|---|---|---|---|---|
| | | | GRADE I | GRADE II | GRADES III AND IV | | | | |
| *Grouped by Sex.*— | | | | | | | | | |
| Male | 25 | 50.3 | 9 | 11 | 5 | 17 | 14.5 | 7 | 5.4 |
| Female | 25 | 51.2 | 5 | 18 | 2 | 19 | 14.3 | 9 | 5.5 |
| *Grouped by Therapy.*— | | | | | | | | | |
| Therapy | 16 | 50.4 | 3 | 9 | 4 | 15 | 14.0 | | 6.4 |
| No therapy | 34 | 50.8 | 11 | 20 | 3 | 21 | 14.5 | | 5.0 |

*"S.I." = Severity index; an arbitrary scale of severity used in our clinic and based on weighted values for age, fundi, level of diastolic pressure, and renal and cardiac complications. Scores over 6 indicate moderately severe disease.

TABLE II. EFFECT OF HYPOTENSIVE AGENTS ON RESPONSE TO NOXIOUS STIMULI

| | SALINE (TEST 1) | | | | COLD PRESSOR (TEST 3) | | | | COLOR (TEST 4) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | INITIAL BLOOD PRESSURE (MM. HG) | | RESPONSE (MM. HG) | | INITIAL BLOOD PRESSURE (MM. HG) | | RESPONSE (MM. HG) | | INITIAL BLOOD PRESSURE (MM. HG) | | RESPONSE (MM. HG) | |
| | MEAN | S.E. | MEAN | S.E. | MEAN | S.E. | MEAN | S.E. | MEAN | S.E. | MEAN | S.E. |
| *Therapy (16 Patients).—* | | | | | | | | | | | | |
| Systolic | 184 | ±6 | 37 | 4 | 189 | 7 | 47 | 5 | 192 | 6 | 28 | 5 |
| Diastolic | 105 | 4 | 15 | 2 | 106 | 4 | 29 | 2 | 108 | 4 | 7 | 1 |
| *No Therapy (34 Patients).—* | | | | | | | | | | | | |
| Systolic | 167 | 5 | 28 | 3 | 175 | 5 | 32 | 3 | 179 | 6 | 17 | 3 |
| Diastolic | 102 | 2 | 11 | 1 | 105 | 2 | 25 | 2 | 107 | 2 | 6 | 1 |
| *p.—* | | | | | | | | | | | | |
| Systolic | | .02* | | 0.1–.05† | | > .05 | | .02* | | > .05 | | .1–.05† |
| Diastolic | | > .05 | | > .05 | | > .05 | | 0.1–.05 | | > .05 | | > .05 |

*Probable significance.
†Doubtful significance.

TABLE III. SCORES ON CLYDE "MOOD SCALE"

| | GROUPS (BY B. P. REACTIONS) | | | | SIGNIFICANT INDIVIDUAL GROUP COMPARISONS (p) | | | GROUPS (BY STATUS) | | | | SIGNIFICANT INDIVIDUAL GROUP COMPARISONS (p) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HYPERTENSIVE | NORMOTENSIVE WITH F. H.* | NORMOTENSIVE — WITHOUT F. H.* | F | HYPERTENSIVE VS. NORMOTENSIVE WITH F. H. | HYPERTENSIVE VS. NORMOTENSIVE WITHOUT F. H. | NORMOTENSIVE WITH F. H. VS. NORMOTENSIVE WITHOUT F. H. | HYPERTENSIVE | MEDICAL STUDENTS | NORMOTENSIVE | F | HYPERTENSIVE VS. MEDICAL STUDENTS | HYPERTENSIVE VS. NORMOTENSIVE | NORMOTENSIVE VS. MEDICAL STUDENTS |
| *Self-Rating Scores.—* | | | | | | | | | | | | | | |
| Friendly | 51.4 | 48.2 | 49.7 | 0.64 | | | | 51.4 | 52.3 | 48.0 | 0.75 | | | |
| Energetic | 46.9 | 47.0 | 48.3 | 0.11 | | | | 46.9 | 50.8 | 43.2 | 2.91 | | | |
| Clear-thinking | 49.8 | 43.6 | 48.5 | 1.53 | | | | 49.8 | 51.6 | 43.5 | 3.14† | | .05 | .02 |
| Aggressive | 49.5 | 47.9 | 49.4 | 0.35 | | | | 49.5 | 50.3 | 46.5 | 0.95 | | | |
| Jittery | 53.5 | 46.9 | 52.7 | 3.32† | .02 | | .10–.05 | 53.5 | 49.6 | 51.1 | 1.60 | | | |
| Depressed | 52.5 | 47.4 | 51.5 | 1.65 | | | | 52.5 | 47.1 | 51.5 | 2.42 | | | |
| *Differences Between Ratings of Investigator and Self-Rating (Negative Values Indicate Lower Score for Investigator).—* | | | | | | | | | | | | | | |
| Friendly | 3.9 | 1.1 | —1.6 | 2.33 | | | | 3.9 | —5.6 | 3.3 | 7.74‡ | .001 | | .01 |
| Energetic | 9.3 | 6.3 | 4.0 | 1.41 | | | | 9.3 | —0.2 | 9.5 | 6.91‡ | .001 | | .01 |
| Clear-thinking | 8.3 | 14.8 | 9.2 | 1.23 | | | | 8.3 | 4.2 | 16.1 | 5.39‡ | | .02 | .001 |
| Aggressive | —1.7 | —3.0 | —0.3 | 0.30 | | | | —1.7 | 0.6 | —3.7 | 1.64 | | | |
| Jittery | —11.5 | —7.4 | —10.0 | 2.27 | | | | —11.5 | —7.9 | —9.4 | 0.95 | | | |
| Depressed | —7.3 | —4.6 | —4.5 | 1.05 | | | | —7.3 | —0.3 | —8.4 | 6.97‡ | .01 | | .01 |

*F. H. = Family history of hypertension.
†F value significant at 5 per cent level.
‡F value significant at less than 1 per cent level.

The differences within the normotensive group when they were divided on the basis of family history were quite striking. Subjects with a positive family history of hypertension showed significantly greater responses of systolic pressure with correspondingly greater elevations in pulse rate to all three tests. Thus, these "prehypertensives" were more reactive, but even with a stimulus predominantly affecting peripheral resistance—i.e., the cold pressor test—the hyperreactivity apparently resulted from an elevation of cardiac output rather than a further increase in peripheral arteriolar constriction. This observation is pertinent to the work of Eich, Peters, and Lyons[9] concerning the mechanisms of early hypertensive disease. Although it is generally accepted that normal cardiac output and increased peripheral resistance are characteristic of established hypertension, these investigators have demonstrated that patients with labile hypertension of brief duration tend to have high cardiac output and normal or even reduced peripheral resistance. In addition to the increased systolic reactivity, our data indicating significantly higher pretest systolic blood pressure in the group with a positive family history are also in keeping with the hypothesis that elevated cardiac output may be an important mechanism in early hypertensive disease.

Remington and associates,[10] in a recent study of the reactivity of children of hypertensive and normotensive parents to four essentially physical stimuli, also noted higher systolic base lines in the positive family history group and commented on the pertinence of this observation to an increased cardiac output or stroke volume in early hypertensive disease. It is of interest that these observers failed to find significant differences in responsiveness of their two groups to the four stimuli, all of which primarily affected diastolic blood pressure. They noted, however, that immediately prior to the cold pressor test the systolic difference between groups was most marked and commented that "this suggests that the blood pressure response to a mental stimulus may be excessive in the potentially hypertensive . . . subject." Our data tend to confirm this suspicion.

The scores on the Clyde Mood Scale failed to demonstrate notable "mood differences" either about self or toward the physician between groups with different pressor responses. On the other hand, differences in Mood Scale were present, particularly in relationship to the doctor, between "volunteer" medical student subjects and patients of all types, in the absence of differences in their pressor responses. Inasmuch as the patients scored the investigator higher in positive categories, these data may indicate that the reaction between investigator and patient subjects remained a doctor-patient relationship, while medical students, as subjects, tended to identify themselves with the investigator.

Although the above interpretations seem to minimize the importance of the doctor-patient relationship in determining blood pressure reactivity, they are clearly subject to the limitations of the Clyde Mood Scale. No data are available to determine how these scores correlate with investigator-subject interactions as determined from techniques affording analysis of attitudes in depth. Certainly much evidence from studies of others as well as previous investigations of our own[1,11] indicates that doctor-patient relationships can profoundly influence the course of hypertensive disease. The Mood Scale did demonstrate a positive

correlation within the hypertensive group between the "jittery" score (anxiety) and the "depressed" score, and the response of systolic blood pressure to the injection of saline. This may indicate that, although the hypertensive patients as a group were not more anxious, the intrinsic mood of the individual hypertensive patient relates to his blood pressure reactivity. However, elucidation of this point must await further understanding of the Mood Scale. Moreover, it should be pointed out that, because of our presently limited knowledge of the applicability of the Mood Scale, we have calculated only those few correlations indicated in our results, choosing those seemingly most clearly related to anxiety. With so many other possible combinations in our data—e.g., 72 in the hypertensive group alone —it is quite possible that the significant associations noted occurred purely by chance.

The observation that patients receiving drug therapy did not demonstrate a diminished pressor response can be interpreted in several ways. The patients were not receiving drugs in a controlled study. It has been demonstrated frequently that apparent pharmacologic effects on blood pressure in hypertensive disease are often placebo effects.[12] Accordingly, treated patients, although receiving dosages in the usually accepted range, may have been subjected to minimal pharmacologic effects and thus remained responsive to noxious stimuli. Second, the lack of consistency in the type of drugs given these patients and in the time of last dosage prior to testing are several factors at least which might influence responsiveness. Finally, some of the drugs were sympatholytic agents and various studies have indicated that peripheral arterioles deprived of autonomic innervation may show increased responsiveness to humoral vasoconstrictor agents,[13-16] a factor of possible importance since Ferris and co-workers[17] have shown clearly that emotional stimuli can operate through humoral as well as neurogenic pathways. In any case, these data suggest the need for study not only of basal blood pressure in patients receiving therapy, but also examination of their response to physical and psychological stimuli. Such information is necessary for basic knowledge of psychophysiologic mechanisms as well as for effective evaluation of drug therapy.

SUMMARY

Although psychophysiologic responses of blood pressure have been studied extensively, the relative importance of the intensity and meaning of the psychological stimulus, as contrasted with intrinsic somatic factors affecting blood pressure change, remains unclarified. Accordingly, a systematic analysis of responsiveness to four relatively simple noxious stimuli was undertaken in 50 hypertensive patients. Normotensive subjects, with and without a family history of hypertension, were also studied. Automatic indirect blood pressure and pulse recording equipment was used.

Hypertensive patients responded to psychological stimuli with marked increases in blood pressure equivalent to those resulting from the cold pressor test, but with significantly lesser effects on peripheral resistance. Neither degree nor systolic/diastolic ratio of pressor responses could be correlated clearly with the assumed intensity and direction of the emotional stimuli. The sex of the

subject, and, to a lesser extent, the age significantly affected responses. Low basal values did not enhance reactivity; in fact certain data suggested a greater rise in systolic pressure with higher initial systolic values. Among normotensive individuals, those with a positive family history displayed enhanced responses to all tests, apparently consequent to an increased cardiac output. A self-administered psychological test based on adjective check lists (Clyde Mood Scale) failed to reveal differences either in patient or in doctor-patient attitudes between groups with different blood pressure responses. Significant differences, however, were displayed between patients of all types and volunteer subjects. A slight correlation between response of systolic blood pressure and anxiety was noted in hypertensive individuals following one of the stimuli.

The results are interpreted to indicate that blood pressure responsiveness may be more specifically conditioned by certain intrinsic determinants than by the nature of the emotional stimulus.

We appreciate the assistance of Dr. Howard Reidbord in the early phases of this study, and of Dr. Robert E. Miller in planning the statistical analyses.

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# Psychiatry

## THE DEVELOPMENT OF PERFORMANCES IN AUTISTIC CHILDREN IN AN AUTOMATICALLY CONTROLLED ENVIRONMENT

C. B. FERSTER, PH.D., AND
MARIAN K. DEMYER, M.D.
INDIANAPOLIS, IND.

*From the Indiana University Medical Center, Indianapolis.*

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THIS experiment reports data from a technique for producing behavior in autistic children[1] under an automatically controlled environment. The experiment is an explicit attempt to develop techniques for enlarging the very narrow range of performances generally present in these children's repertoires. Performances were developed and maintained in order to determine some facts about these children's existing repertoires, and to discover what potentiality exists for extending them. We created each child's repertoire by arranging specific consequences to his performance (reinforcement) which increased the subsequent frequency of those performances. Early in the experiment, the reinforcements which were delivered were food, candy, and trinkets*; later, coins were delivered which could be cashed in for various other rewarding consequences.

The experiment involved pressing a key. This simple arbitrary act was chosen because: (1) The response took little time or effort to execute, and it left the child in a position to respond again. The frequency with which the child pressed the key could therefore vary over a wide range, from a few responses per hour to several thousand. Such a dependent variable is potentially sensitive to many independent variables, and gives a continuous measurement of their effects. (2) A performance such as pressing a key actuates an electrical contact and hence can be objectively and automatically recorded. It also permits the automatic programing of the entire experiment, so that all of the experimental procedures can be arranged precisely and without error. Extended training and long-term exposure to the conditions of the experiment which would be impossible manually become possible because the experiment is carried out by automatic devices. Over 50,000 coins were delivered and 400,000 responses recorded for Subject 1 alone. (3) The frequency of key pressing is intuitively analagous to the major problem in the measurement of human behavior: measuring the child's

This project was supported by Smith Kline & French.

*Assortments of trinkets were purchased from the Penny King Co., 2538 Mission St., Pittsburgh, Pa., and Plastic Processes, Inc., 83 House Ave., Freeport, N. Y.

disposition to behave; the probability of his acting. A simple recording of whether the child acted or not gives little information about his general tendency to behave. A single occurrence of an act may be caused by a strong or a weak repertoire. The child's disposition to act can vary from low to quite high, and the level of motivation is best determined by examining the frequency of key pressing; the child's disposition to engage in the experimental behavior is recorded as the frequency of occurrence of the key press. (4) The use of an arbitrary response, such as pressing a key, has been used extensively in animal experiments dealing with general problems in maintaining behavior of the organisms. Many of the processes discovered have proved to be phylogenetically general among a wide range of mammals, including man; and this information may be used to determine when we have established normal control over the child's behavior. Recording of the behavior as the effect of the animal's performance on an electrical switch makes possible the comparisons of the performance of a wide range of species.

These tendencies have already been used successfully in the study of the behavior of normal children.[2,3] One of the problems in developing experimental techniques for creating new behaviors in these children and maintaining old ones is the development or discovery of reinforcers which are powerful enough to sustain large amounts of behavior. The problem of a reinforcer is especially acute with the autistic child because of his general deficit in positively maintained behavior. The frequency with which the child presses the key, particularly when it is reinforced only intermittently, provides a technique whereby new and more effective reinforcers can be discovered. By observing which experimental procedures increase and decrease the frequency with which the child presses the key, an experimental environment can be constructed which becomes increasingly effective in supporting strong behavior in the child. A major accomplishment of the research reported here is the development of procedures which can strongly maintain the behavior of a child under conditions where the form of the behavior occurs explicitly as a result of the experimental procedures.

A durable reinforcer is especially necessary for the development of complex behavior. While the child is being exposed to the development of new complex performances, nonreinforcement of inappropriate responses is inevitable. This nonreinforcement weakens the performance; and if the new behavior is to be developed, the child must continue to emit the performance first. After the child's performance can be sustained in the experimental environment, it should become possible to investigate many aspects of the autistic repertoire which have heretofore been inaccessible. The child's auditory and visual repertoires could be studied if various stimuli were presented to him while at the same time reinforcement was differentially given or withheld, depending upon which stimulus was present. The ability of the child to come under the control of the relevant stimuli would be shown by the differential performance in the presence of the various stimuli.

Complex forms of behavior could be developed after the child has begun performing by successively approximating more complex activities. Reinforcements can be shifted in the direction of the complex form of activity required.

Once the child's performance conforms to the new condition of reinforcement, the contingency is again subtly shifted. Ultimately, studies of even such complex forms of behavior as speech may be carried out by reinforcing vocal sounds in the child's repertoire and gradually approximating more and more complex forms.

*Subject 1.*—The first subject is male, and was 8 years old and in good physical condition at the start of the experiment. Speech occurred at the later part of his first year, and proceeded to sentences of two or three words. Motor development and coordination were good. According to parental reports, the child's illness began when he was 18 months old. The father was under strong financial pressure, holding a job while maintaining a farm, and at the same time experiencing considerable ill health. The parents spent evenings "barking" at each other. During the period of development of the boy's illness, the mother was subject to severe depressions, usually stemming from arguments with her husband and sometimes lasting for several days. During these depressions, she was almost completely inactive, paying nearly no attention to the subject beyond minimal care. The subject began taking off clothing unpredictably, tearing down curtains, upsetting furniture, pounding his head against the wall, and wandering 2 or 3 miles from home. The father's ways of dealing with the boy's disturbances ranged variously from severe punishment to isolation; he built a fenced-in cage to control the subject's increasingly destructive behavior. Speech began to diminish at this time, and the child has been practically mute since the age of 4, when the parents sought medical care. At 7 years, the child was admitted to the LaRue D. Carter Memorial Hospital. During his stay there he remained nonverbal, except for rare occasions when he spoke one or two words. He characteristically tore his clothing and broke toys and articles belonging to other children. Severe tantrums that had no relationship to current events occurred frequently. He spent long periods of time simply standing idly, lying on the floor, or shuffling through the ward. His most frequent activities consisted of agilely climbing on objects and playing with water and clay. He also spent large amounts of time smearing and mouthing clay or candy. His performance during his stay at the hospital had changed little before the experiment described here.

*Subject 2.*—The second subject is a female who was 9½ years old at the start of the experiment. The girl developed normally until she was about 3, when she began to lose speech, play destructively with toys, smear feces, and lose bladder and bowel control. She became phobic in regard to animals. Some speech remained, however. From the age of 19 months to 3 years, an adolescent high school girl was the subject's constant companion. The adolescent handled the subject completely permissively and with much "babying." The mother was passive and allowed the adolescent to take over all of her functions. The subject's behavioral difficulties began when the adolescent girl left and the mother became pregnant with a second child.

Neither subject showed any evidence of brain damage in standard neurological and EEG examinations at the time of admission or subsequently.

*Control Subjects.*—Control subjects were inpatients in the Children's Service who did not appear to have any intellectual deficits and were essentially normal except in respect to the general level of social control. The control subjects were approximately the same ages as Subjects 1 and 2.

*First Exposure to the Experiment.*—When Subject 1 was first exposed to the experiment, only the single-column vendor was present (Fig. 1). During the first session, an attendant who knew the subject led him to the experimental room and gave him candy. During the second session, the subject found candy that had been previously placed in the trough of the vending machine. During the third session, the candy was delivered remotely by the solenoids on the vending machine; and during the fourth session, the key was installed, with every press of the key operating the vending machine. Several sessions later, the subject entered the room alone.

With Subject 2 the eight-column vendor, the pigeon, phonograph, and pinball machine were present. The subject was brought to the room by an attendant whom she knew, and all of the devices were demonstrated. The session was

completed with the attendant in the room. Starting with the second session, the subject was placed in the room alone, the door locked, and the normal procedure carried out.

Except at the beginning of the experiment, Subject 1's experimental duration was 60 minutes or 80 reinforcements, whichever occurred first. The duration was increased to 90 minutes on the seventieth session. Subject 2's experimental duration was 90 minutes throughout.

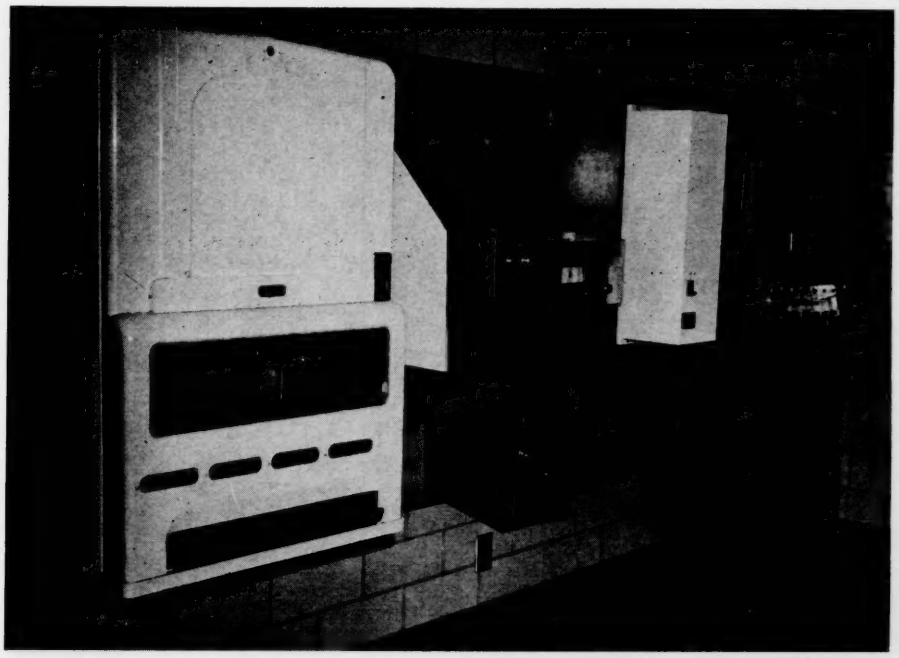

Fig. 1.—Photograph of the experimental room. The eight-column vendor is at the extreme right, the single-column vendor on the left. The other devices on the wall, from left to lower right, are phonograph and color wheel. Above the color wheel is the coin dispenser with the coin key and the coin trough. The other two devices were installed subsequently to the experiment reported here. The pigeon is not shown.

*Reinforcing Devices.*—Food appeared to be the most effective reinforcer available. Nevertheless, an attempt was made to establish a more durable reinforcer by delivering a coin that in turn could be used in a wide variety of reinforcing devices. The experimental use of the coin parallels its use in the normal social environment.[4] It is an occasion which makes possible other behavior producing a variety of reinforcers. Such a conditioned generalized reinforcer has the advantage that it derives its reinforcing effect from other reinforcers which are effective under various kinds of deprivation. Should the level of deprivation in respect to several of the specific reinforcements used in the experiments be low, the generalized reinforcer would continue to maintain behavior through the remaining devices which might be relevant to current deprivations. If the

number of reinforcing devices were large enough so that at least some of these would be reinforcing for each subject, the same experimental room could be used for a number of subjects. There is also the possibility that the generalized reinforcer may have its effect by the sum of the specific reinforcers.

The children operated the reinforcing devices in the room either by pressing a key or depositing a coin. The key was a telephone-type lever switch, mounted in a translucent plastic panel which could be lighted from behind. A solenoid gave an audible click whenever the switch was sufficiently depressed. When the key was inoperative (before and after the experimental sessions and during time out) the clicker and light were disconnected. The coin slots resembled those ordinarily found on vending machines, except that small pilot lights next to them indicated when the slots were operative. Coins deposited when the coin light was off were recorded but did not operate the device. The coins were stainless-steel discs the size of a 1-cent piece. Reinforcing devices were added gradually during the early stages of the experiment. Tables I and II give the exact points of introduction of the reinforcing devices.

*Coin Dispenser:* The coin dispenser and key were mounted together in a wall unit. The coins were delivered to a tray just below the response key.

*Single-Column Vendor:* The single-column vendor, a modified pastry-vending machine, was operated by solenoids which emptied the compartments of the six columns of the machine in sequence. When the vendor's 80 compartments were emptied, the light next to the coin slot went out.

*Pigeon:* A transparent plastic wall unit, 12 by 12 by 14 inches, contained a hungry pigeon and associated devices so that the bird pecked at the disc only when the light was on. A coin deposited in the coin slot turned on the lights in the apparatus so that the child could observe the bird's performance for 30 seconds.

*Phonograph:* An aluminum box, approximately 12 by 12 by 8 inches, contained a speaker, a coin slot with an associated light, and a light that came on whenever the phonograph was operating. When a coin was deposited in the slot, the phonograph, which was located in the adjoining room, played through the speaker for 30 seconds. A coin deposited in the coin slot while the phonograph was on reinstated the full 30-second period. The records were generally lively marches or children's records. The material was varied from day to day, and was a rough attempt at presenting records of interest to the child.

*Pinball Machine:* The pinball machine simulated a baseball game with many moving parts, bells, flashing lights, etc. Depositing a coin in the coin slot of the pinball machine released two balls for play.

*Eight-Column Vendor:* The eight-column vendor was adapted from a cigarette machine by installing solenoids, and an independent coin switch and coin light on each column. Part of the face of the machine was made of Plexiglas so that the subjects could inspect the kind of candy in each column. When a column became empty, its coin light went out. When the whole vending machine was inoperative, all of the coin lights were extinguished. The eight-column vendor was operated with coins only.

*Color Wheel:* The color wheel consisted of three discs, each red, blue, and yellow, rotating on a common shaft and in respect to each other, and driven by a variable-speed motor. The result was a kaleidoscopic color change. The subject would vary the speed of the motor by turning a knob on the face of the panel, thus changing the kaleidoscopic color effects. A coin in the slot whenever the light was on provided operation of the color wheel for 30 seconds.

*Organ:* A portable electric organ was modified by installing a rod which locked the keys until the solenoid was released. A coin in the coin slot freed the keys for 30 seconds.

*Food, Candy, Toys, and Trinkets Delivered in the Vending Machines.*—In general, the kinds of candy, crackers, and foods delivered were varied during different phases of the experiment, and between subjects, depending upon their preferences. Candy and food delivered included candy corn, M & M's, peppermints, chocolate mints, Tootsie-Rolls, raisins, dried apricots, burnt-sugar-coated peanuts, marshmallows, various kinds of crackers and cookies, plain chocolate, and chocolate-covered raisins. The single-column vendor was used to deliver small trinkets, 1-ounce portions variously of fruit juice, water, and milk in covered plastic containers, candy, crackers, and some larger toys, such as Tinker toys, miniature cars and harmonicas, and blocks. The trinkets were selected from a large assortment and were changed daily.

*Schedules of Reinforcement.*—The schedule of reinforcement describes the program by which the experimentally recorded performance operates the reinforcing devices.[5]

*Fixed-Ratio Schedule (FR).*—Every *n*th response activates the reinforcer. This schedule normally produces a high, sustained rate of responding. When the number of responses required for reinforcement is increased, responding stops after reinforcement, followed by an abrupt shift to the high rate.

*Variable-Interval Schedule (VI).*—Passage of time determines when a response activates the reinforcer. The average interval between reinforcements is specified, but the actual intervals vary from reinforcement to reinforcement. This schedule normally produces a moderate, roughly constant rate of responding.

*Multiple Fixed-Ratio, Variable-Interval Schedule.*—The color behind the key changes between red and green after each reinforcement. When the color is red, the coin is delivered by the *n*th (e.g., fifteenth) response. When the color is green, the first response after a variable period of time produces a coin. The performance that normally emerges from each color is appropriate to the schedule of reinforcement in its presence.

## PLAN OF THE EXPERIMENT

Tables I and II contain a detailed summary of the experimental procedures for Subject 1 and Subject 2, respectively. These specific procedures were in effect for the session numbers indicated in the first column. The second column refers to the schedule by which pressing of the key produced coins. The third column indicates the session at which the various reinforcing devices were introduced,

TABLE I. SUMMARY OF EXPERIMENTAL PROCEDURES FOR SUBJECT 1

| SESSIONS | SCHEDULE OF REINFORCEMENT (COINS) | REINFORCING DEVICES* | | | | | | | STIMULUS CONTROL | ILLUSTRATIONS | GENERAL FACTORS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SINGLE-COLUMN VENDOR | 8-COLUMN VENDOR | PIGEON | PHONOGRAPH | PINBALL | COLOR WHEEL | ORGAN | | | |
| 1–21 | VI† 7–30 (candy and coins) | | | | | | | | | Fig. 2 | Sparine 50 mg. t.i.d. |
| 22–30 | Multiple VI FR | Coins | | | | | | | | | |
| 31 | FR‡ 9 | | | | | | | | | | |
| 32–37 | VI 30 | | | | | | | | | Fig. 3 | Sparine discontinued. Thorazine 50 mg. t.i.d. |
| 38–39 | | | | | | | | | | | |
| 40–44 | | | | Coins | | | | | 10 sec. time out after reinforcement | Fig. 4 | |
| 45 | FR 15 | | | | Coins | | | | | | |
| 46–49 | | | | | | | | | 10 sec. time out after reinforcement<br>Multiple CRF. extinction 15–60 sec. after regular session | Figs. 5, 6 | |
| 50–56 | Key Disconnected | | | | | | | | Multiple CRF. extinction 30–60 sec. in coin slots | | |
| 57–70 | FR 13 | | | | | Coins | | | Coin slot operative every 2nd-5th coin, 15–75 sec. | Fig. 8 | |
| 71–78 | Mult VI 60″ FR 13 | | | | | | | | Coin slots operative continuously except when a column is emptied | | |
| 79–81 | | | Coins | | | | | | | Figs. 9, 10, 11, 12 | |
| 82–85 | FR—Mult—FR etc. | | | | | | | | | | |
| 86–94 | FR 15 | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 95–104 | | | | | | | | Coin slot operative every 2nd-3rd coin for 20 sec. | | Tantrums and frequent atavisms |
| 105–128 | | Crf | | Crf§ | Crf | Crf | | Coin slots operative continuously except when a column is emptied | Fig. 13 | |
| 129–137 | FR 2–5 | | | | | | | | | Pinworm infection. Tantrums and frequent atavisms |
| 138–146 | FR 15 | | | | | | | | | Experimental room remodeled. Pacatal 50 mg. t.i.d. Tantrums and frequent atavism |
| 147–187 | FR 4–5 | | | | | | | | | Electrical shock discovered and removed. Thorazine 25 mg. t.i.d. Session 171. Pacatal 50 mg. h.s. Compazine 10 mg. t.i.d. Session 179 |
| 187–198 | | FR 2 | | FR 2 | FR 2 | FR 2 | Crf | Coin slots operative every 2nd or 3rd coin for 30 sec. | Fig. 15 | |
| 199–204 | | | | | | | | Coin slots alternately operative and inoperative every 30–40 sec. | | |
| 205–215 | | | | | | | | As above coin in inoperative slot extends inoperative period | | |
| 229–235 | FR 8–15 | | | | | | | As above—coin in empty column makes entire vendor inoperative | | |
| 236–239 | FR 5 | | | | | | | | | |
| 240–244 | FR 15 | | | | | | | | | |
| 245–251 | FR 1–2 New Key | Coins | Coins | Coins | Coins | Coins | Coins | | | |
| 252–256 | FR 15–25 | | | | | | | | | |
| 257– | FR 2 New Key | | | | | | | | | |

*Schedule of reinforcement by a key mounted directly on the device.
†Variable interval.
‡Fixed ratio.
§Continuous reinforcement.

TABLE II. SUMMARY OF EXPERIMENTAL PROCEDURES FOR SUBJECT 2

| SESSIONS | SCHEDULE OF REINFORCEMENT (COINS) | REINFORCING DEVICES* | | | | | | | STIMULUS CONTROL | ILLUSTRATIONS | GENERAL FACTORS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SINGLE-COLUMN VENDOR | 8-COLUMN VENDOR | PIGEON | PHONOGRAPH | PINBALL | COLOR WHEEL | ORGAN | | | |
| 1–5 | | | | | | | | | 10 sec. time out after reinforcement | Fig. 7 | |
| 6–17 | FR 15 | | | | | | | | Coin slot operative every 2nd-5th coin | | |
| 18–37 | | Coins | Coins | Coins | | | | | 10 sec. time out after reinforcement | | Compazine 10 mg. b.i.d. |
| 38–45 | FR 2–5 | | | | | | | | | | Pinworm infection discovered and treated. Piperazine for 2 weeks |
| 46–53 | FR 2–15 | | | | | | | | | | Compazine discontinued. Thorazine† |
| 54–56 | | | | | | | | | | | Pharyngitis. Electric shock discovered and removed. Thorazine ‡, § |
| 57–91 | FR 1–5 | FR 2–7 | | FR 2–4 | FR 2–4 | FR 2 | Crf | Crf | 8-column vendor coin slots operative every 2nd coin | | |
| 92–100 | | | | | | | | | | Fig. 14 | |
| 101–103 | | Coins | | Coins | Coins | Coins | Coins | Coins | | | |
| 104–136 | FR 8—FR 15 | | | | | | | | 8-column vendor coin slots alternately operative 30 sec., inoperative 10–40 sec. | | 102° F. fever, Session 114¶ |
| 137–143 | FR 5 | | | | | | | | | | |
| 144–149 | FR 15 | | | | | | | | | | 103.8° F. fever, tonsilitis, Session 149 |
| 150–155 | FR 2—Paper-drive | | | | | | | | | Figs. 16, 17, 18 | |
| 156–162 | FR 15–30 | | | | | | | | | | |

*Schedule of reinforcement via a key mounted on the device.
†Thorazine 25 mg. t.i.d. and h.s.; 3 days later, 40 mg. t.i.d. and 60 mg. h.s.; 3 days later, 50 mg. t.i.d. and 100 mg. h.s.
‡25 mg. t.i.d. and 50 mg. h.s.
§Session 77, 25 mg. t.i.d. and 50 mg. h.s.
¶Rectal temperature.

and whether they were operated by a coin or by a lever mounted directly on the device. The fourth column, "Stimulus Control," indicates the presence or absence of stimuli correlated with conditions of reinforcement, e.g., the lamp which is on when the coin slot can be operated by a coin. Abbreviated procedures are explained in more detail in the footnotes following the tables.

The experimental procedures are grouped into the following phases.

*Subject 1.—*

*Phase 1, Sessions 1 to 30:* During this period, the general technique was developed, reinforcers discovered, and the experimental procedures integrated with the ward routine. A stable key-pressing performance was developed on a variable-interval schedule of reinforcement.

*Phase 2, Sessions 31 to 70:* The schedule of reinforcement with coins was changed from variable interval to fixed ratio. Both subjects performed appropriately to the control normally produced by the fixed-ratio schedule.

Key pressing was brought under the control of the lights behind the key by periodically turning off the lights and discontinuing reinforcement. Both children stopped pressing the key when the light was off. Control by the coin lights was developed similarly. The coin light was only periodically lighted, and coins deposited when it was off were wasted. In another procedure, designed to make the subjects accumulate coins before using them, the coin light came on for a brief period with every *n*th coin delivered (e.g., 3). Coins deposited as soon as they were received (except for the *n*th coin) were wasted. During this period, the children's performances were weaker than those previously recorded. However, this was at least in part because both children had a pinworm infection and had received accidental electric shocks delivered by the experimental devices.

*Phase 3, Sessions 71 to 104:* Here, intermittent reinforcement of the behavior was emphasized, in order to determine the degree to which large amounts of behavior could be sustained with minimal reinforcement. The stimulus control by the coin light which had developed previously with the one-column vendor was lost when the eight-column vendor was introduced. There were many tantrums during this period, and the recorded performance became considerably weaker.

*Phase 4, Sessions 105 to 165:* Because of this weakened performance, the schedules of reinforcement were made optimal by delivering coins on small fixed-ratios and operating all of the reinforcing devices except the eight-column vendor directly by one or two presses of the key mounted directly upon the device. At Session 138, all of the reinforcing devices except the electric organ, had been installed.

*Phase 5, Sessions 166 to 186:* During this period, the pinworm infection was cured and the electric shock was eliminated, the schedules of reinforcement remained optimal, and strong performances were recovered.

*Phase 6, Sessions 187 to 235:* The control by the coin lights was re-established by additional coin-saving procedures.

*Phase 7, Sessions 236 to 239:* The reinforcing devices were operated only by coins, with the direct levers removed. The size of the fixed-ratio was reduced to facilitate the transition.

*Phase 8, Sessions 240 to 261:* During this period, the number of wasted coins approached zero, and a performance was maintained with the use of the coin as a generalized reinforcer at larger fixed ratios.

*Subject 2.*—Experimentation on Subject 2 began some months after that on Subject 1, so that nearly all of the reinforcing devices had been already installed at her first experimental session. Fewer procedural apparatus changes were required for Subject 2 because of her generally more advanced behavioral repertoire, and because some of the experimental problems had been solved with the first subject.

*Phase 1, Sessions 1 to 37:* The first development of a performance occurred in these sessions. Stimulus control was developed by the lights associated with the coin switches and keys.

This subject came under the control of these contingencies very rapidly; and, in general, the procedures developed with the first subject were sufficient to generate the required performance during the early sessions.

*Phase 2, Sessions 38 to 104:* A severe pinworm infection was discovered and treated at the start of this period, and at Session 53, a high-voltage shock between the floor and the reinforcing devices was discovered. By Session 91, the effects of the shock disappeared. During this phase, all of the reinforcing devices were operated by direct levers except for the eight-column vendor, which still was operated by means of coins.

*Phase 3, Sessions 105 to 162:* All of the reinforcing devices were operated through coins produced by pressing the key, and the schedule of reinforcement by coins was increased first to 15, then to 25. Stimulus-control procedures remained in force during part of this period.

## RESULTS

*First Development of a Performance.*—

*Subject 1:* Fig. 2 shows the continuous development from a weak performance at the start of the experiment to a well-sustained performance by the twelfth session. Only the single-column vendor with the key mounted on it was present. Compartments of the vending machine were loaded with either candy, food, or a coin. When a coin was delivered, it could be deposited in the coin slot, thereby operating the next compartment.

The child's responses are graphed against time, and the marks oblique to the record indicate the occurrence of a reinforcement. The scale of the record is given by the grid at the right of the figure. Coins are delivered on a variable-interval schedule whose mean interval of reinforcement was increased progressively during the first session. Each segment is a record of the entire daily session. The amount of responding increased progressively over the sessions, reaching an over-all rate of approximately 15 responses per minute.

Fig. 3, Records A through E, continues the next sessions on VI 30, and shows a fall in the over-all level of responses until the performance reaches a low, constant rate just sufficient to produce reinforcements roughly on schedule. Part of

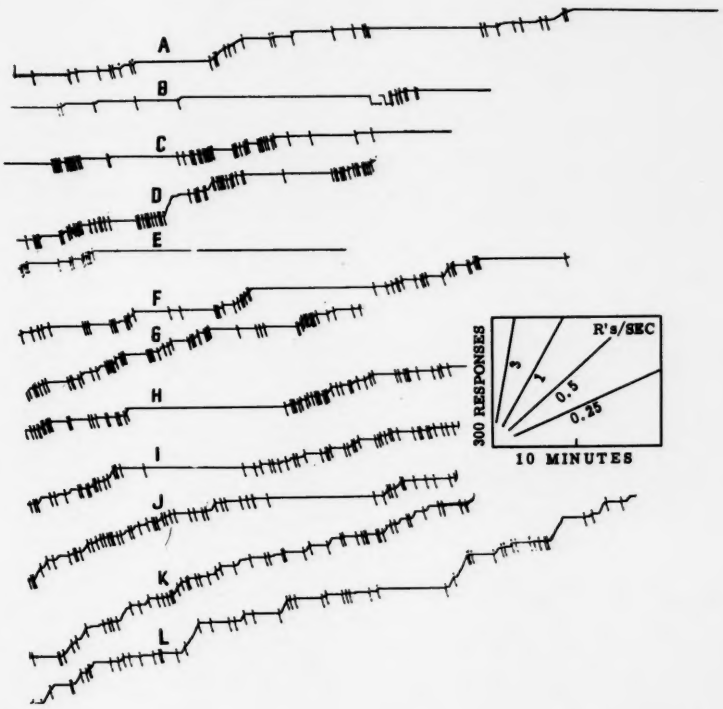


Fig. 2.—Cumulative records of the first 12 sessions of the experiment under variable-interval reinforcement. Records *A-E*, VI (variable interval) 7 (seconds); Records *F-H*, VI 10; Records *I-K*, VI 25; Records *K-L*, VI 30.

the fall in the over-all rate of responding was produced by "ritualistic" climbing over the top of the machines which occurred between presses of the lever.

Beginning with the fourth session (Record D), a coin dispenser was installed inside the vending machine and the lever delivered only coins. These coins in turn operated the vending machine through its coin slot. Records F through L continue the twenty-second to the twenty-eighth session of the experiment when the schedule of reinforcement had been changed to multiple FR 5 blue, VI 30 red. There was no evidence that any differential performance emerged during the red and blue colors corresponding to the different schedules of reinforcement. However, the performance was sustained over the 60-minute experimental session with a steady emission of behavior, and no pauses longer than a minute or two occurred. Much of the pausing involved time spent eating the candy. Approximately 200 to 400 responses were emitted per session. Key presses were frequently followed by the ritualistic climbing behavior, as in the early parts of the record. By the end of this period, this subject ate the candy as he received it, without the previous smearing, licking, and other kinds of handling.

*Transition to Fixed Ratio and Development of Stimulus Control by Time Out After Reinforcement.—*

*Subject 1:* Fig. 4 describes the development of the fixed-ratio performance

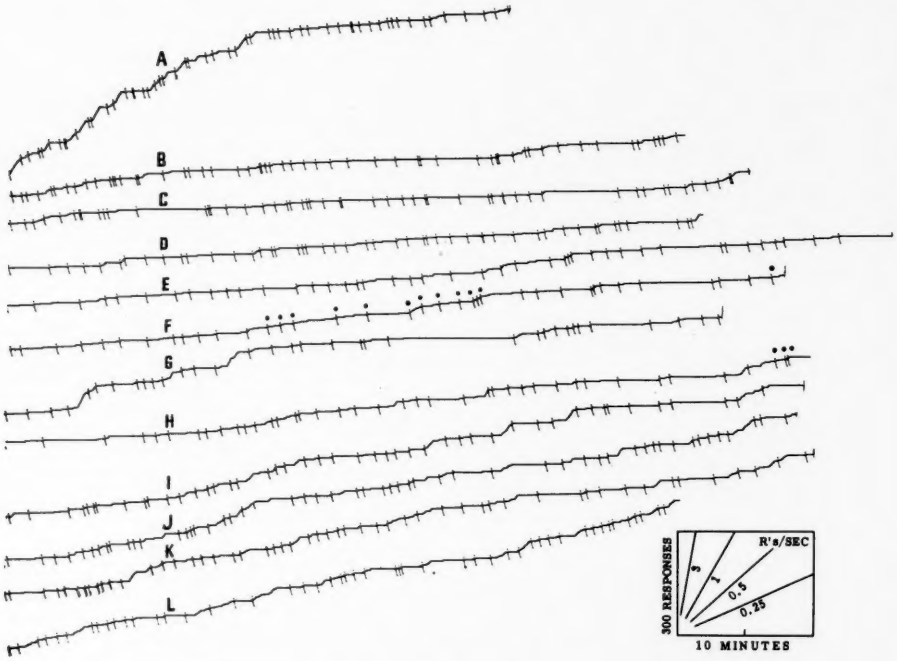


Fig. 3.—Final performance on variable interval 30 reinforcement and transition to multiple FR 5 VI 30 reinforcement.

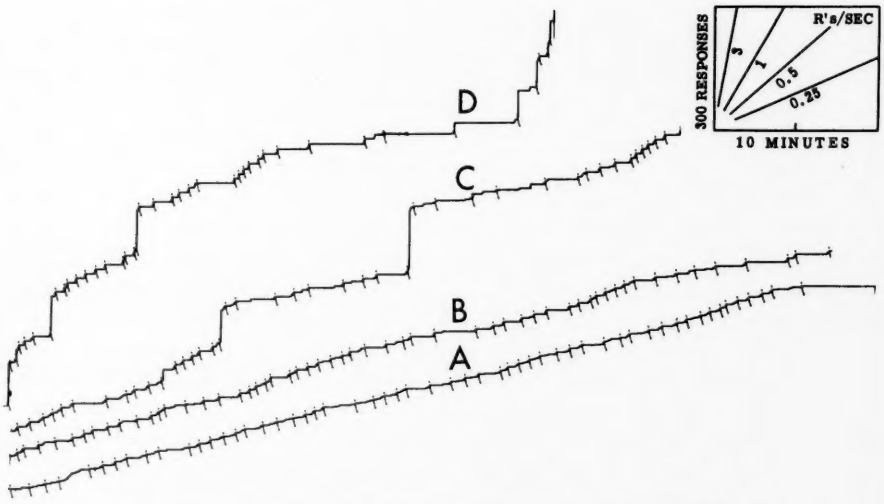


Fig. 4.—The development of the characteristic performance under FR 9, and the effect of a time out following reinforcement.

on the thirty-eighth session after the previous reinforcement on this variable-interval schedule. The fixed-ratio reinforcement soon altered the performance, producing its characteristic pattern of responding: sustained responding at small fixed ratios; pausing, when it occurs, after reinforcement; and an abrupt shift from pausing to the high fixed-ratio rate. The ritualistic climbing which occurred on the variable-interval schedule disappeared almost immediately on the fixed-ratio schedule. This sudden loss of the climbing occurs because it no longer accidentally reinforces as in the variable-interval schedule, where the probability of reinforcement increases after time spent climbing. The order of the records in the figure is inverted for more compact presentation. The fixed-ratio schedule of reinforcement was in force beginning with the fifth reinforcement of Record A. Records A and B, the first two sessions under FR 9, showed a very rapid development of the fixed-ratio pattern. By Record B, most of the responding occurred in sustained bursts; and in frequent instances, responding began immediately after the delivery of a coin. Any pauses tended to occur just after reinforcement. Beginning with Record C, a 10-second time out (lights out, keys inoperative) occurred after each coin delivery. Any response occurring during the time out extended the time out its full duration to facilitate the development of the discrimination. The frequency of pressing the key when the light was out first increased as the new fixed-ratio program increased the over-all responding and then gradually declined (Fig. 5) as the light behind the key came to control the child's performance. The graphic recorder did not run during the time out, so that the nonreinforced responding is evident in the vertical segments of the records. The amount of nonreinforced responding reached a peak of approximately 1,800 responses. Five sessions later (Record F), no responses occurred during the 10-second time out following each reinforcement. In addition to the nearly perfect control by the stimulus behind the key, the child performed almost continuously during the 60-minute experimental session.

During the one hundred nineteenth session, an extinction curve after reinforcement on FR 15 was recorded, where the coin dispenser jammed so that no further coins were delivered but the solenoid continued to operate normally. This extinction curve, shown in Fig. 6, indicates another aspect of normal control by the fixed-ratio schedule of reinforcement. The pauses after reinforcement disappeared, representing the time that would ordinarily be spent in using the coins; and a high rate of responding was sustained for over 600 responses, followed by no further responding for the remaining 40 minutes of the experimental sessions.

*Subject 2:* This subject began using all of the devices in the room almost immediately, and quickly performed appropriately to the fixed-ratio schedule of reinforcement. Fig. 7 shows records of the first four sessions after continuous reinforcement. The over-all level of responding is high and sustained in the first session, but falls progressively thereafter. The pigeon could be operated directly by a key mounted on the pigeon box. The subject operated the pigeon apparatus once in Record B and 26 times in the session represented in Record D. The lower rate of responding is partly attributable to interference from activity around the trained pigeon. Only the eight-column vender was present at this time, and it

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was almost immediately controlled by the coin lights associated with the eight coin slots. A 10-second time out occurred after each coin delivery. (The recorder did not run during the time out.) This subject showed no tendency to press the key during the 10-second time out after reinforcement.

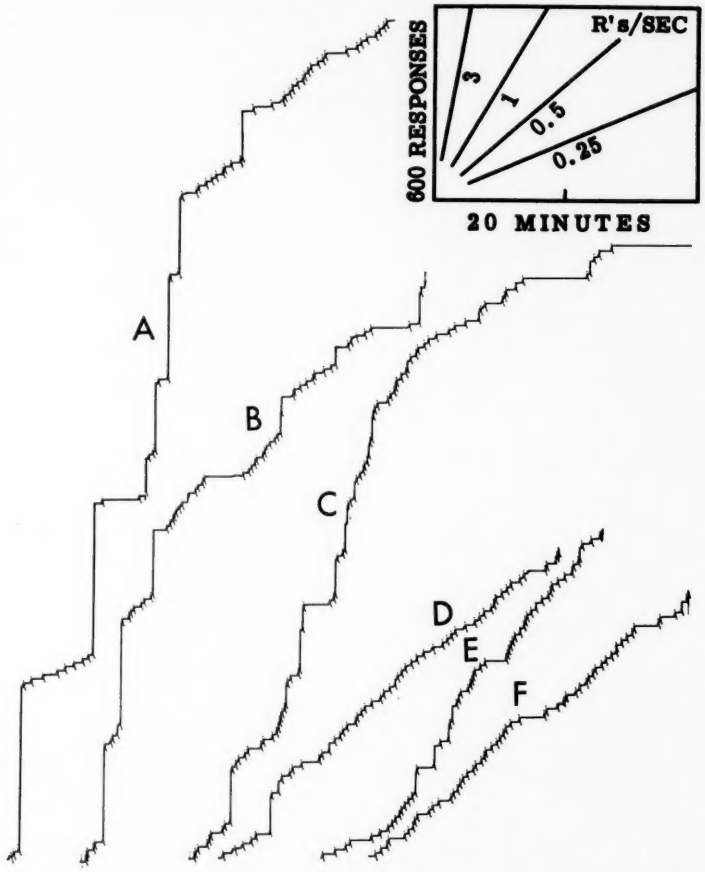


Fig. 5.—Subject 1. Decline in response during the time out after reinforcement.

Beginning with the sixth session, the coin-saving procedure was put into effect. Every second coin delivered lighted the coin-slot lights for 30 seconds. Coins deposited when the lights were out were wasted. The procedure is the same as the one used previously by Kelleher[6] in the study of conditioned reinforcement in chimpanzees. Subject 2 soon stopped placing coins in the inoperative coin slots when the coin lights were off. During the eighth to the twelfth sessions, the numbers of coins deposited in inoperative coin slots of the vending machines were 2, 4, 2, 14, and 4, respectively.

*Development of Stimulus Control by the Coin Light.*—

*Subject 1:* In an attempt to bring the behavior of depositing coins in the coin slot under the control of the coin light, Subject 1 was given, variously, 200 to 250

free coins at the end of the regular experimental session beginning with Record D of Fig. 5, and for four sessions thereafter. In the presence of the coin light, appearing every 15 seconds (later 30, and then 60 seconds), a coin deposited in the slot produced candy. Coins deposited in the vending machine when the coin light was out postponed the inoperative interval, and did not produce candy. The subject continued to place coins in the inoperative slot, and there was no evidence of any control of behavior by the light. For the next eight sessions, the regular experimental procedure was discontinued. After seven sessions, a small degree of control by the coin light began to emerge. Of the 110 coins deposited in the various devices, 56 produced reinforcement, 54 were deposited while the light was out, 6 were used in the pigeon device, 15 were used in the phonograph, and the remainder went in the single-column candy-vending machine.

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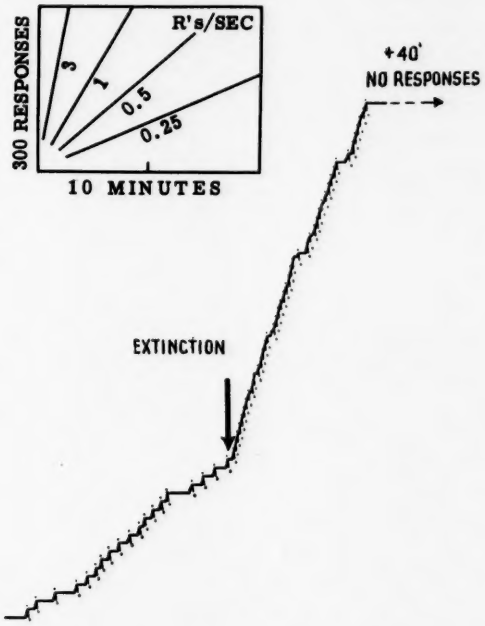


Fig. 6.—Subject 1. Extinction after reinforcement on FR 15. At the arrow, coins are no longer being delivered, although the coin dispenser makes its characteristic sounds.

The development of the control by the coin light was continued by reconnecting the key and arranging the coin-saving procedure described above for Subject 1. The coin-slot lights were made to appear for 15 seconds after every second coin that was delivered. The coin-saving procedure was continued for 14 sessions, during which the coin-slot lights were made to come on after 3, 4, and 5 coins, progressively. The successful development of this technique makes it possible to record the key pressing uncontaminated by the intervening behavior with the reinforcement (e.g., eating). Pauses are difficult to interpret because they may be caused by either a disinclination to respond or time spent consuming the reinforcement.

During the first eight sessions of the coin-saving procedure, the subject inserted coins in the coin slots as soon as they were received, whether or not the coin light was on. Thereafter, the coin-light control began to emerge in the 6 sessions represented in Fig. 8. The performance is sustained throughout the session and the child is performing continuously, either pressing the key and receiving coins, or using coins in the various devices. In Record A, the coin light appears after every second coin; 39 of the 77 coins received during the session

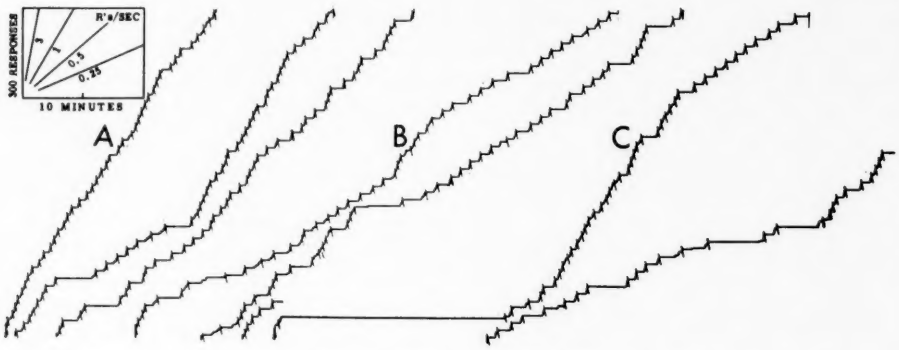


Fig. 7.—Subject 2. The first four sessions of the experiment. The schedule of reinforcement is FR 15.

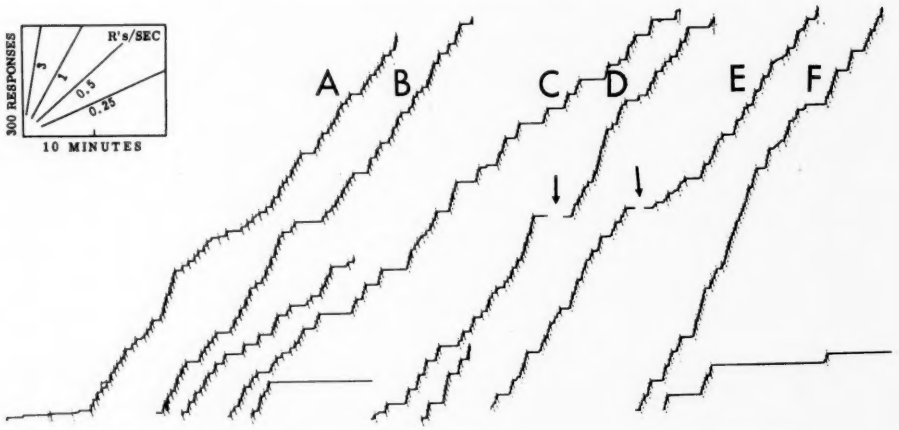


Fig. 8.—Subject 1. Performances recorded under FR 15 when the light above the coin slot began to control the subject's performances.

were deposited while the coin light was on and 38 when it was off. This performance is typical of the previous sessions on the same procedure. Beginning with Record B, however, the subject saved coins delivered when the coin light was off, and deposited them later when it came on again. Of the 113 coins received during this session, 34 were deposited with the coin light off. In Record C, every third coin produced the lighted coin slot for 45 seconds, and only 9 of 89 coins received were deposited when the coin slot was inoperative. In the following

session, in Record D, only 7 coins were wasted. A 23-minute pause occurred at the arrow. In Record E, all 84 coins received were deposited while the coin slot was operative. A 14-minute pause occurred at the arrow. In Record F, every fourth coin produced the coin light correlated with the operative coin slot, and eight coins were deposited in the inoperative coin slots.

The pinball machine was present for the first time and demonstrated to the subject in Record F, but it was not used. On the following session, however, with the pinball machine continuously operative, he played without interruption for 52 minutes.

In the following session, when the pinball machine could be operated only by a coin in the coin slot, 52 coins, of a total of 90, were deposited in the pinball machine. Much smiling and vocalizing of the form "Da-da-da," "Ba-ba-ba" occurred. The movement of the balls produced considerable excitement, and the subject frequently sat on the machine, following its action and the course of the balls. The detailed attention to the operation of the pinball machine disappeared progressively during the ensuing months.

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*Subject 2:* The second subject's performance on the coin-saving procedure showed almost perfect control by the coin lights of the vending machine from the very start of the procedure.

*Performance Under Multiple VI 60 Second FR 13 (Subject 1).*—In his first exposure to the multiple schedule, the subject responded appropriately to the fixed ratio in the variable-interval color, and hence emitted many more responses for reinforcement than usual. The normal control by this schedule—fixed ratio performance in the one color and a variable-interval performance in the second color—never developed. Probably as a result of the decrease in the frequency of reinforcement, the over-all rate of responding fell, reaching the values seen in Fig. 9, containing the sixth to the ninth sessions on the multiple schedules. By the eighth and ninth sessions, Records E and F, the over-all performance levels were among the lowest recorded in the experiment. The fall in the level of responding was also caused by the introduction of the eight-column vendor. When the subject emptied a column of the vendor, he continued to deposit coins in the same column even though the coin light went out when the last compartment of the column was emptied. The previously developed control by the coin lights did not transfer to the eight lights and coin slots of the eight-column vendor.

*Transition Between Fixed Ratio and Multiple Fixed Interval, Fixed Ratio.*—The effect of the multiple schedule of reinforcement in weakening the subject's performance was explored briefly by alternating between blocks of the simple fixed-ratio schedule and the multiple schedule. In general, the subject's performance was well-sustained under the fixed-ratio schedule and weak under the multiple schedule. Record A of Fig. 10 begins with only the fixed-ratio schedule; at the arrow, the schedule was changed to the multiple schedule. A high rate of responding occurs under the fixed-ratio schedule, and carries over in the multiple schedule for approximately the next 10 minutes, after which it falls sharply to nearly zero by the middle of the session. In the next session, shown in Record B, responding is sustained, as typical with the start of a session; but when the schedule is switched to fixed ratio, the severe decline in rate that usually occurs toward

the end of the session is eliminated. In the third session (Record C), beginning on the fixed ratio schedule, responding is sustained with little pausing and high rates. When the schedule is changed back to the multiple schedule at the arrow, responding ceases for the remaining 50 minutes of the session except for two brief periods. During these sessions, the subject continued to place coins in the empty (unlighted) columns of the vending machine, even though this kind of control had developed earlier in the experiment with the single-column vendor.

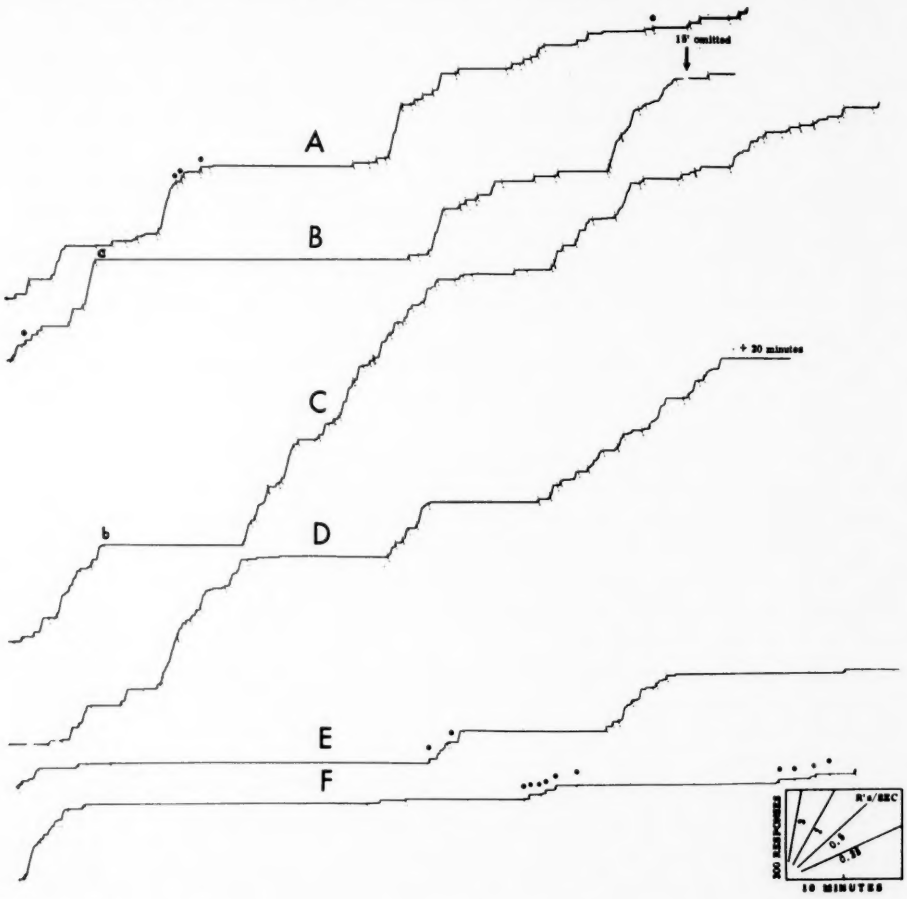


Fig. 9.—Sessions 6 through 9 on the multiple schedule. The dots above the curves indicate when coins were used in the pinball machine.

*Extended Reinforcement on FR 15 and an Attempt to Increase Low Performances by Optimal Conditions of Reinforcement.*—

*Subject 1:* Fig. 11 shows the number of coins delivered to Subject 1 from the eighty-sixth through one hundred twenty-eighth sessions and some of the details of their use. The first part of the figure to Session 104 represents performances when responding is weakened because large numbers of coins are wasted in

inoperative coin slots. The remaining sessions represent an attempt to strengthen the performances in the experimental room by providing optimal conditions of reinforcement.

The procedures used between Sessions 86 and 104 reflect the large number of coins wasted in inoperative (unlighted) coin slots. From the ninety-fourth through ninety-ninth sessions, 35 to 175 coins are wasted per session. The performance becomes weak between the ninety-ninth and one hundred fourth sessions, when the largest number of coins delivered was 30 (Session 101); and no coins were delivered during two sessions. Most of the coins in the non-food devices were used in the pinball machine. The non-food devices were, in general, not used.

The period of the experiment represented in Fig. 15 was characterized by atavistic behavior, tantrums, and frequent disruption of the performances normally generated by these experimental procedures. During Sessions 99 to 103, the subject used the sharp edge of the coin to scrape slivers from the Plexiglas surface of the pinball machine and spent whole sessions marring the surface of these two devices. The child stopped scraping the Plexiglas only when the edges of the coins were smoothed.

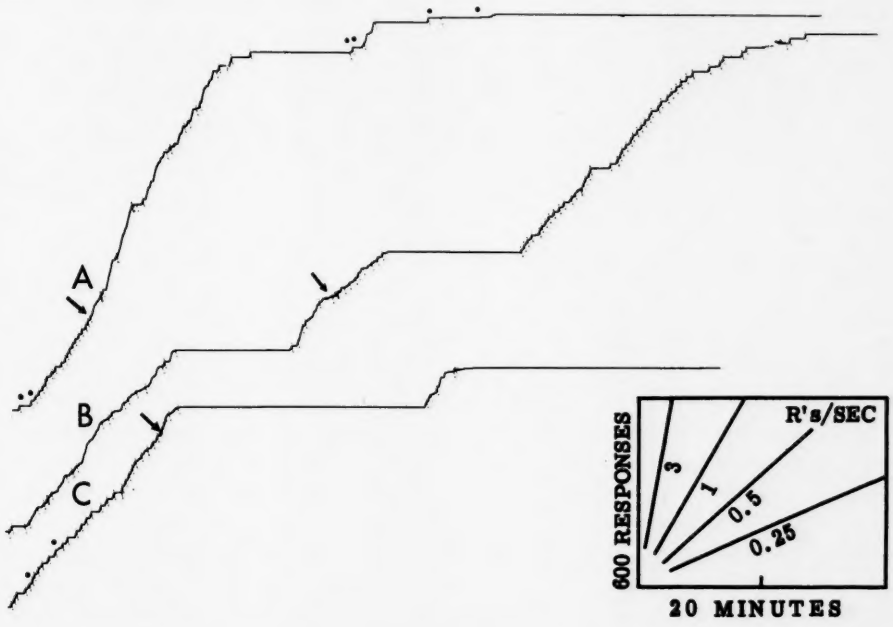


Fig. 10.—Subject 1. Transitions between the fixed-ratio and multiple schedules. The dots above the curves indicate when coins were used in the pinball machine.

When the performance deteriorated at about Session 100, keys were mounted on the face of each non-food device. A single press of the key operated the device. The single-column vendor (also operated by a key) was reintroduced, delivering trinkets, fruit juice, crackers, and toys. Under these more favorable reinforcement schedules, the number of coins increased to values comparable with those in the

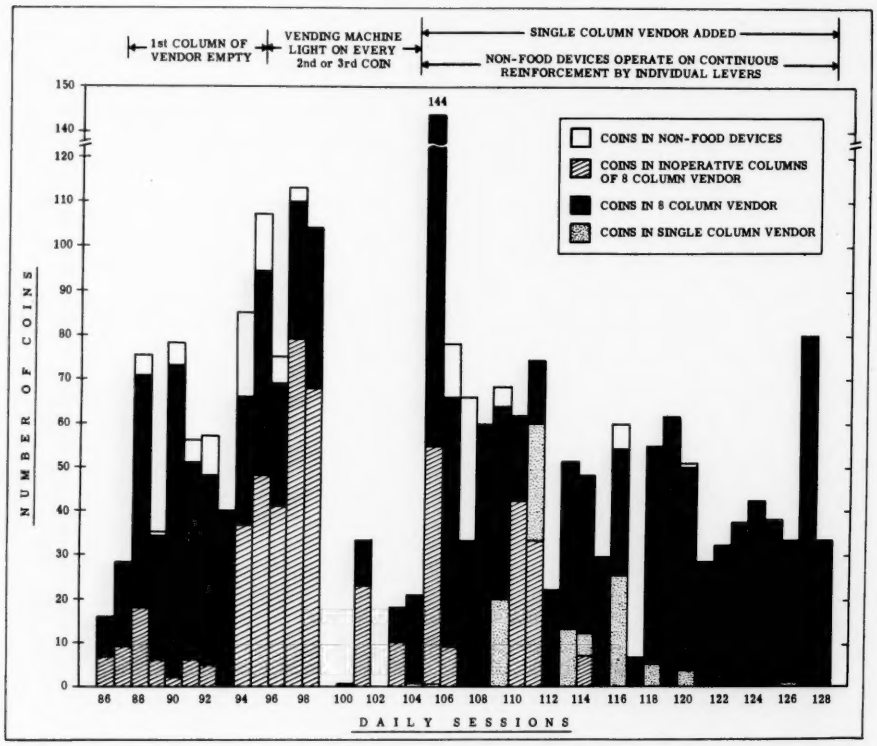
1st COLUMN OF VENDOR EMPTY
VENDING MACHINE LIGHT ON EVERY 2nd or 3rd COIN
SINGLE COLUMN VENDOR ADDED
NON-FOOD DEVICES OPERATE ON CONTINUOUS REINFORCEMENT BY INDIVIDUAL LEVERS
144
COINS IN NON-FOOD DEVICES
COINS IN INOPERATIVE COLUMNS OF 8 COLUMN VENDOR
COINS IN 8 COLUMN VENDOR
COINS IN SINGLE COLUMN VENDOR
NUMBER OF COINS
0 10 20 30 40 50 60 70 80 90 100 110 120 140 150
86 88 90 92 94 96 98 100 102 104 106 108 110 112 114 116 118 120 122 124 126 128
DAILY SESSIONS

Fig. 11.—Subject 1. Summary of the performance during the period when it is weakened by large numbers of coins wasted in an inoperative coin slot.

eighty-sixth to ninety-ninth sessions; but large numbers of coins were still wasted when a column of the eight-column vendor became empty. Toward the end of the period shown in the figure, the subject began to vary the column in which he deposited coins. No columns were emptied; hence, very few coins were wasted. During this period, the non-food devices, including the single-column vendor, were hardly used, even though the subject had to press a key only once to operate any of them. After periodic previous demonstrations, the phonograph was demonstrated again during the one hundred twenty-sixth session, and the subject began pressing the key mounted on the phonograph device. At Session 129, the severe pinworm infection was discovered and treatment was begun. It is not known for how long the infection had been present, but the period is presumed to have been at least 2 to 3 weeks.

Fig. 12 gives details of the performances represented in Fig. 11, ranging from the well-sustained performance in the one hundred fifth session, where the subject is continuously performing during the entire session, to the one hundred seventeenth session, when only 7 coins were received. Toward the end of the one hundred fifth session, a column failed to deliver candy because of an equipment failure even though the coin light was on. After wasting many coins in the inoperative but lighted coin slot, the subject finally ceased responding and returned

to scratching the Plexiglas on the pinball machine. A severe tantrum occurred during the last part of the session (*a* to *b* on the record), even though the vending machine was operating at this time. The subject went through the normal performance in the midst of shouting, screaming, and head banging. The subject was in the midst of a severe tantrum when he was taken from the ward to the experimental room at the start of Session 117. During a pause in the tantrum, the subject noticed the experimenter and went along quietly to the experimental room. He spent most of the session lying on the floor and on top of the pinball machine. Except for the few coins received, there was little activity of any kind except a brief period, of about 15 minutes, of looking at the pigeon, smiling and saying "A-a-a-a" in drawn-out syllables.

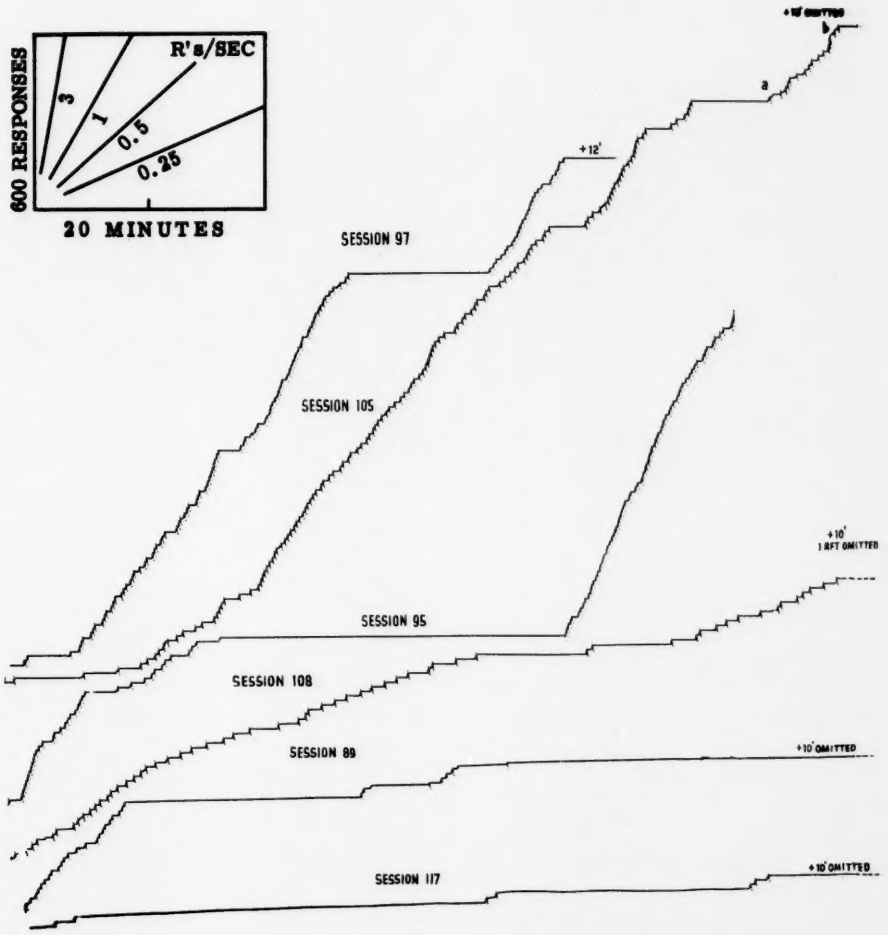


**Fig. 12.—Subject 1. Cumulative curves of representative daily experimental sessions taken from the period of the experiment shown in Fig. 11.**

During the third session, the subject began putting coins in a slit in one wall of the experimental room during a tantrum that increased in intensity with each of the 10 or 12 coins that were deposited. He then hammered on the door with increasing intensity during the 20-minute pause in the middle of the session. After a short period of quietly sitting on the floor by the door, he resumed the sustained activity recorded at the end of the session.

Fig. 13 summarizes the main facts of the experiment from Sessions 129 to 166. These performances show the effects of the electric shock, the recovery from the pinworm infection, and the continued lack of development of the stimulus control by the coin-slot lights. The over-all performance varies markedly from day to day, but is, in general, sustained. Responding occurs about equally among the eight-column vendor, the non-food devices, and the single-column vendor.

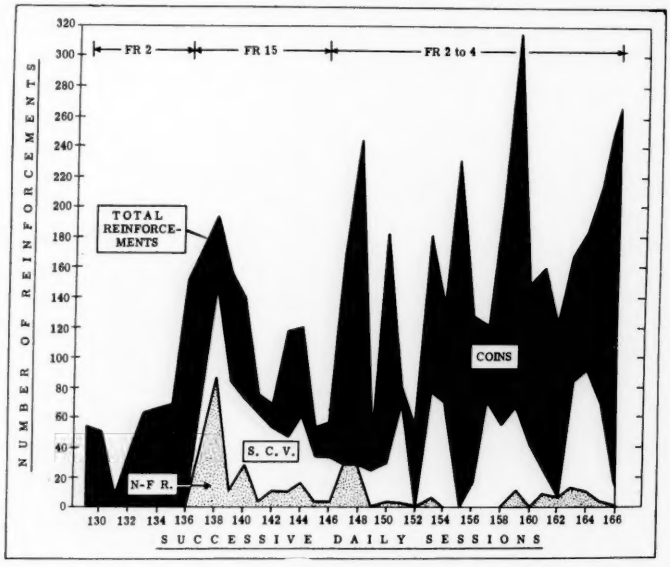


Fig. 13.—Subject 1. Summary of performances from the period when they are being affected by electric shock, pinworm infection, and continued lack of development of control by the coin-slot lights. *S.C.V.*, Single-column vendor; *N-F R.*, Non-food reinforcements.

The pinworm infection discovered on the one hundred twenty-eighth session was treated, and was probably gone by the one hundred thirty-eighth session. The exposed voltages were discovered on the one hundred forty-fifth session and were removed, and the effects of the shock were probably gone by the one hundred sixtieth session. Except for the one hundred thirty-eighth to one hundred forty sixth sessions, the schedule of coin reinforcement was kept very optimal in order to sustain the subject's performance. All of the non-food reinforcing devices, as well as the single-column vendor, continued to be operated by keys mounted directly on them. Fig. 17 records the total number of reinforcements received rather than responses or coins. In general, the non-food reinforcing devices are scarcely used; and most of the activity produces candy from the eight-column vendor by coins, or trinkets and candy from the single-column vendor through

the key mounted on the face of the unit. On the one hundred forty-fourth session, the subject withdrew his hand from the trough of the coin dispenser as if he were getting a shock, and then began using his shirt tail to take the coins from the trough. He also began to deposit coins in the green vendor by holding them in his shirt tail to insulate himself from the eight-column vending machine. During this period, this child responded in bursts, so that coins accumulated in the coin trough, occasionally falling to the floor. Many of the coins delivered during this period were not used. Even though the electric shock had been eliminated by the one hundred forty-sixth session, the subject continued to accumulate coins rapidly until the one hundred sixtieth session, taking only those falling on the floor and using his shirt tail to deposit them in the eight-column vendor. The apparatus was probably delivering shocks between the one hundred thirty-fifth and one hundred forty-sixth sessions.

Frequent tantrums and generally large amounts of atavistic performances occurred: for example, urinating over the various devices; head banging; screaming; smearing candy into the various orifices of the room; and reversion to the older pattern of eating candy by rolling it into a ball and licking it from the hands, floor, etc., rather than placing discrete pieces in the mouth and chewing them. Most of the non-food reinforcements occurred about equally among the pigeon, color wheel, pinball machine, and phonograph. The subject used a variety of compartments from the eight-column vendor; but during those sessions when the larger number of coins was deposited, he wasted many coins in empty columns. Numbers of coins wasted in various sessions occurred as follows: Session 159, 45 coins; Session 161, 24; Session 162, 36; Session 163, 16; Session 164, 23; Session 165, 55; and Session 166, 144.

*Subject 2:* Fig. 14 contains an over-all summary of Subject 2's performance from the sixty-fourth to ninety-eighth sessions. The graph gives the number of reinforcements occurring among the various devices. These performances occurred when all of the reinforcing devices were present and were operated via direct keys, and after the pinworm infection and the effects of the electric shock had been eliminated.

Subject 2's behavior, controlled more by the non-food devices than that of Subject 1, was distributed about equally among the phonograph, color wheel, and pigeon. The pinball machine was not used. Consistent with the higher level of the non-food devices, this subject used the single-column vendor (delivering trinkets) more than the first subject. The large number of reinforcements in Sessions 96 to 98 occurred largely on direct keys on the color wheel and phonograph.

*Final Development of a Performance.—*

*Subject 1:* Fig. 15 summarizes redevelopment of control by the lights above the coin switches and the final development of a performance for the remaining 85 sessions of the experiment. The curve at the top of the black area gives the number of coins wasted in empty columns (C. E. C.) or when the vendor is off (V. O.). The curve over the stippled area gives the number of coins wasted when the whole vending machine is off. The number of coins deposited in inoperative slots falls slowly, reaching near zero around the two hundred fiftieth session. Control by the coin lights when the whole vendor is off develops before the

stimulus control by a single empty column. Before the end of the period, all of the devices operate by coins rather than by direct keys (Session 236); and the performance in the experimental room continues to be maintained under the conditions of a generalized reinforcer, although the over-all level of activity is lower. The procedures by which Subject 1 learned to deposit coins only when the lights were on were as follows:

1. Sessions 188 to 197: The coin light came on for 30 seconds at every second, then at every third coin that was delivered. Coins deposited when the lights were off were wasted. The subject continued to deposit coins when all of the vending lights were on. The coin lights flashed on and off at 1 cycle per second.

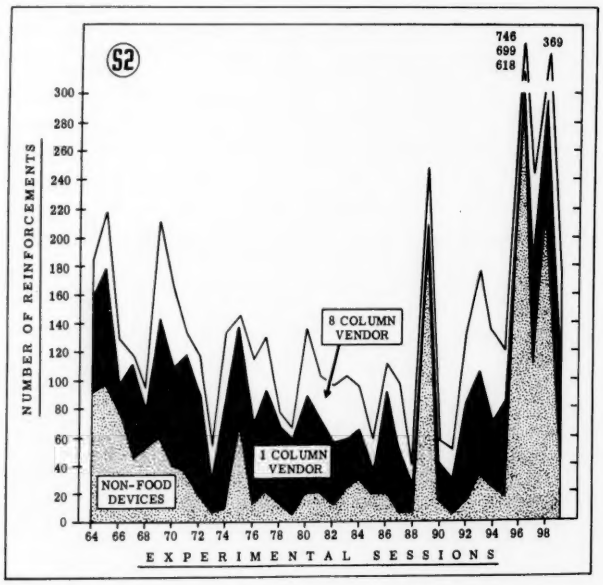


Fig. 14.—Subject 2. Summary of performances during a period when all of the reinforcing devices were operated by direct keys.

2. Session 198: The coin lights were lighted on a time basis rather than after a fixed number of coins as before. Coins deposited when the coin light was out delayed their coming on again. This procedure immediately reduced the number of coins deposited when the whole vendor was off, but did not change the number of coins deposited in empty columns.

3. Session 214: Coins deposited in empty columns shut off the whole vendor for 40 seconds, a mild punishment. Further coins deposited when the vendor was off extended the inoperative period its full duration as before. The number of coins deposited in the inoperative coin slots then began to fall, reaching zero by the two hundred fifty-fourth session. The number of coins wasted is roughly proportional to the total number of coins being deposited.

The schedule of reinforcement and the manner in which the coins were received varied from time to time during this period of this figure. Until the two hundred twenty-ninth session, all of the reinforcing devices (except the

eight-column vendor) operated by direct keys rather than coins. Beginning with Session 229, all of the keys were made inoperative and the reinforcing devices operated only by depositing coins. The schedule of reinforcement was reduced to FR 5 at the same time, in order to ease the transition to the generalized reinforcer; but it was increased to 15 with Session 240, when it was apparent that the performance could be sustained with the generalized (conditioned) reinforcer. From the two hundred forty-fifth to the two hundred fifty-first sessions, coins were delivered by new keys designed to explore the child's perceptual repertoire. These data are presented here only in respect to the continued development of the stimulus control on the vending machine. From the two hundred fifty-second to two hundred fifty-sixth sessions, the schedule of reinforcement was increased progressively to 15, the original key was restored, and the performance was examined under the slightly larger ratios.

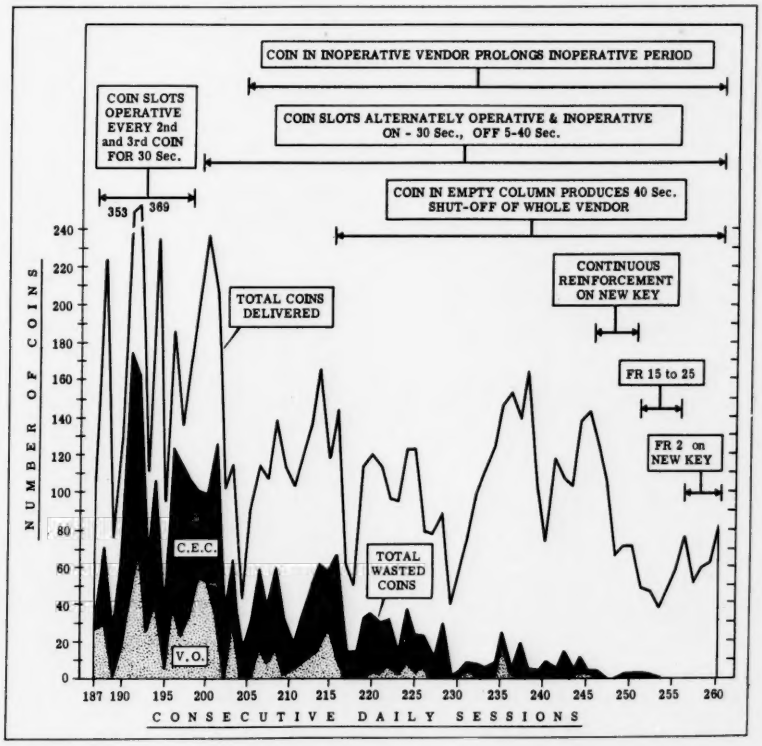


Fig. 15.—Subject 1. An over-all summary of the use of coins showing the development of stimulus control by the coin-slot lights.

The new key and the shift to the coin as a generalized reinforcer have produced a general decline in the total number of coins received. During the last 10 sessions reported in the figure, for example, the over-all level of activity is considerably lower than it was previously, especially when we consider that earlier parts of the graph do not show performances on the devices operated directly through levers.

*Subject 2.*—Fig. 16 contains the comparable performance for Subject 2 from Sessions 100 to 162. The number of coins received and their distribution in the various reinforcing devices is recorded. All of the devices operated through coins instead of by direct key as with the first subject. For the first part of this period, most of the coins were used in the non-food devices: the pigeon, phonograph, and color wheel. Table III gives the median and interquartile range for these devices. Approximately ⅓ of the coins were used for candy from the eight-column vendor, and only a small number in the single-column vendor. During the end of the period from the one hundred fifty-sixth to one hundred sixty-second sessions, the performance shifted more heavily in the direction of the single-column vendor, with a corresponding reduction in the number of coins in the eight-column vendor. The break in the curve after Session 143 indicates a period when a new key, not relevant to the material of this report, was used. In general, the performance is sustained at the small as well as at the large fixed ratios, although the rate of responding is slightly lower on the latter ratios. This subject's performance was controlled almost perfectly by the coin lights. Fig. 17 contains four consecutive performances at the end of this period (Sessions 143 through 146), showing in more detail the continuous manner in which the performance is sustained in this subject. The performance is fairly continuous during the 90-minute session, except for occasional long pauses, as, for example, at the end of the second and fourth sessions shown on the figure.



TABLE III. DISTRIBUTION OF PERFORMANCES ON THE NON-FOOD DEVICES DURING SESSIONS 100-162 (SUBJECT 2)

| | PHONOGRAPH | PIGEON | COLOR WHEEL |
|---|---|---|---|
| $Q_1$ | 36 | 1 | 1 |
| *Median* | 51 | 2 | 3 |
| $Q_3$ | 75 | 9 | 12 |

This subject sustained even the higher fixed ratios in a similar manner. Fig. 18 shows the three consecutive sessions (158 through 160) when the fixed ratio was 25, and the performance remains characteristic of the ratio schedule.

*Control Subjects.*—Each of three control subjects received a 5-minute explanation of the manner of operation of all of the devices. The door was then closed, and the session continued as with Subjects 1 and 2. All of the devices were operated by coins. Records A and B of Fig. 19 contain performances on FR 30 for 2 of the subjects, a girl and boy, approximately the same ages as Subjects 1 and 2. The performance conforms to the typical fixed-ratio pattern, with pauses after some reinforcements and an abrupt shift to the prevailing rate. Responding continues throughout the session, and the performance is sustained better than the best record of the experimental subjects. The coins received were used in all of the vending devices. At this time, the devices present were as follows: phonograph, single-column vendor, pigeon, pinball machine, color wheel, electric organ, television set, train, and eight-column vendor.

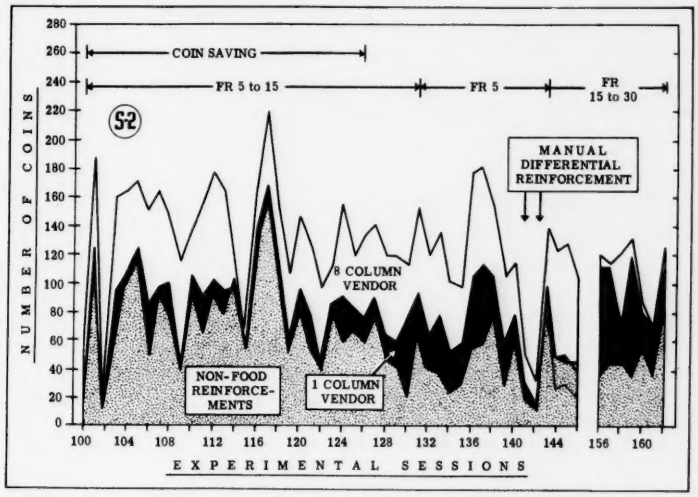


Fig. 16.—Subject 2. Summary of the use of coins and over-all level of performance during the final phase of the experiment.

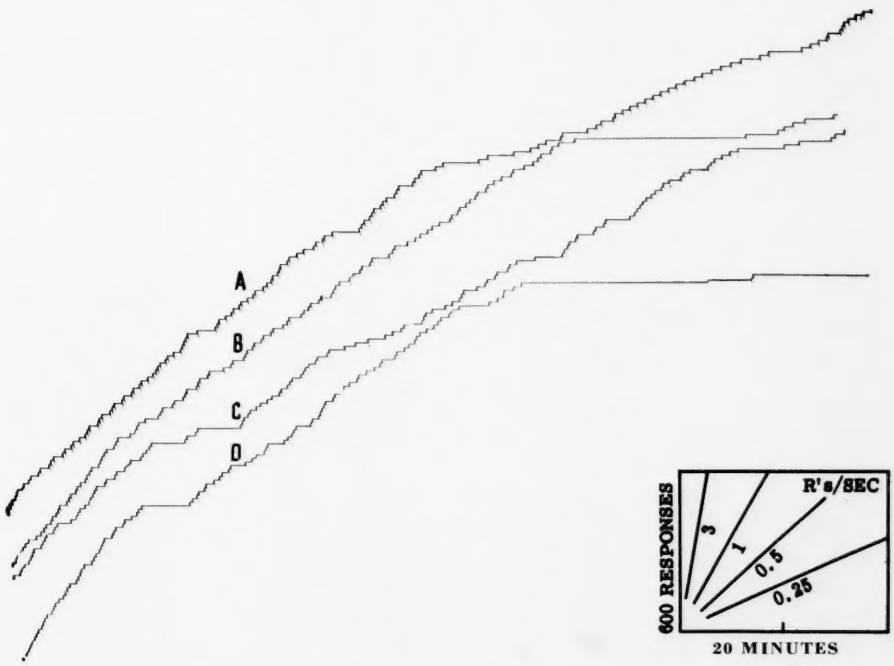


Fig. 17.—Cumulative-response curves showing four consecutive daily sessions on FR 25 toward the end of the period represented in Fig. 16.

Table IV shows the distribution of the total number of coins used by each of the three subjects among the various devices during the entire session. The records in Fig. 19 show only the first 45 minutes of each experimental session. For the remaining 45 minutes, the subjects operated another type of key relevant to an experiment to be reported elsewhere.

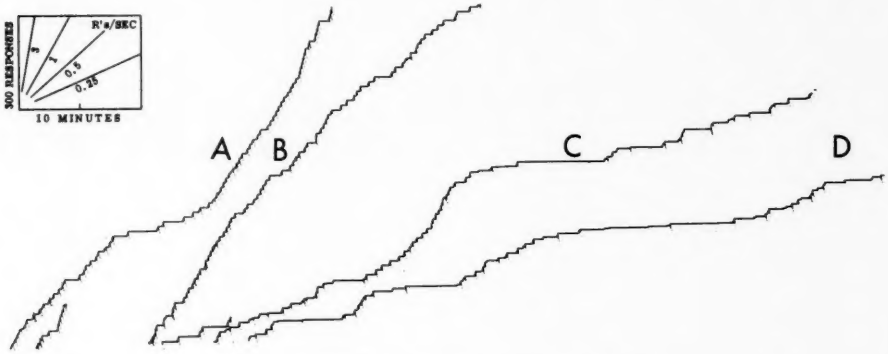


Fig. 18.—Subject 2. Final performance on FR 30.

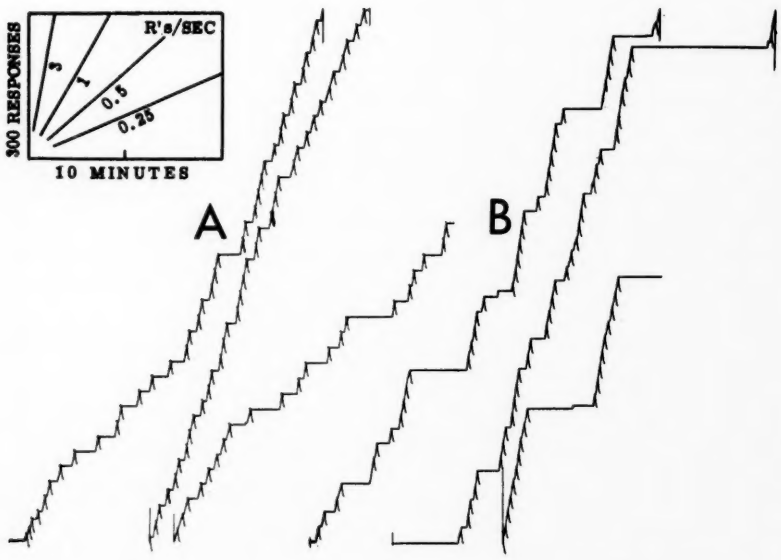


Fig. 19.—Control subjects. Cumulative curves for three subjects showing the first performances in the experimental room with all of the reinforcing devices operated by coins (FR 30).

TABLE IV. NUMBER OF REINFORCEMENTS DELIVERED AND THEIR DISTRIBUTION AMONG THE VARIOUS DEVICES (CONTROL SUBJECTS)

| SUBJECT | 1 | 2 | 3 |
|---|---|---|---|
| Single-column vendor | 77 | 42 | 82 |
| Eight-column vendor | 47 | 28 | 10 |
| Pigeon | 5 | 11 | 8 |
| Pinball | 18 | 50 | 35 |
| Color Wheel | 3 | 3 | 3 |
| Organ | 5 | 2 | 2 |
| Television | 5 | 32 | 5 |
| Train | 17 | 5 | 13 |
| TOTAL | 177 | 173 | 158 |

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## DISCUSSION

The major result of the experiment is a technique for sustaining and objectively recording performances of autistic children. During many phases of the experiment, performances were sustained continuously up to 90 minutes, with no indication that this was a limit. These performances were under the control of reinforcers and other stimuli programed by the various devices in the experimental room. Altering the reinforcement program produced corresponding changes in the children's performance, similar to the efforts of those procedures in animals and normal subjects.[2,7]

The results of these experiments confirm the observations that these children have small and narrow behavioral repertoires. The performance in the experimental room developed slowly during the experiment and in contrast to that of control subjects, who responded quickly and appropriately to all the devices in the experimental room.

Both autistic children's performances showed that their behavior could be brought under control of stimuli by the following basic processes:

1. Reinforcement: The frequency with which the subjects responded was increased by using reinforcers such as food, music, candy, etc.

2. Schedule of reinforcement: Both the fixed-ratio and variable-interval schedules of reinforcement produced their normal and characteristic effects on the child's performance. The accidental reinforcement of responses during the periods of interval reinforcement and the loss of this "superstitious behavior" under fixed-ratio reinforcement demonstrated another aspect of normal control.[8]

3. Stimulus control: New stimuli, if present when a response would produce reinforcement and absent when it went unreinforced, came to control whether or not the child performed. Subject 2 came under the control of the relevant stimuli very rapidly. Subject 1 showed a slow development of stimulus control comparable, at least in form, with performances recorded with animals.

4. Conditioned and generalized reinforcer: The delivery of a coin was a conditioned reinforcer in maintaining the performances recorded, and the coin was also used to actuate a wide variety of reinforcers in the manner of a generalized reinforcer.

The control of the subject's performance by the coin-switch light and the light behind the key is of technical importance. For example, the reinforcing value of the coin could be manipulated by turning out the relevant lights, thus restricting the use of various reinforcing devices. Also, the child's performance could be conveniently interrupted by turning off the lights behind the key. When reinforcing devices with limited capacity became empty, the particular device could be discontinued simply by turning off the coin light while letting the rest of the experiment continue. Furthermore, some performances could be punished by the turning out of the key light.

Both subjects emitted more of the experimentally developed behavior with continual exposure to the automatic environment. Conversely, they spent less time in tantrums of inactivity while in the experimental room. The final level of performances on the non-food devices may not have been possible without the gradual accumulation of experience in the experimental room.

The use of the coin as a generalized reinforcer was a second major technique developed here. By the end of the experiment, the experimental performances could be sustained in both subjects by the delivery of coins.

The 2 autistic subjects showed large differences in their experimental performances. Subject 2, who has more speech and a wider behavioral repertoire than Subject 1, quickly came under control of nearly all of the experimental procedures. The fixed-ratio schedule of reinforcement generated the typical fixed-ratio performance rapidly. This subject very quickly came to respond appropriately to the lights which signaled changes in procedure, as, for example, the lights above the coin slots and the lights behind the key. In contrast, Subject 1 came under the control of the coin lights only after one hundred or more experimental sessions. The 2 subjects differed also in the extent to which they used non-food devices in the room. The performance of Subject 1 was largely maintained by the delivery of food and candy, while that of Subject 2 was maintained by the non-food reinforcers, particularly the phonograph. The differences between the 2 children are closely related to the amount of speech present, probably because the verbal repertoire, by itself, represents a large potential of control by the environment.

Subject 1's slow development of stimulus control suggests that his perceptual repertoire is minimal. Both the time out after reinforcement and the coin lights came to control the subject's performance slowly, as compared with a normal subject, or even an animal. Even after the coin lights controlled the subject's behavior during the first part of the experiment, the repertoire was so minimal that similar lights on the eight-column vendor had no effect until after one hundred or more hours of training. The differences between the two machines were sufficient to completely break down stimulus control which had developed with the single-column vendor. The general complexity of the eight-column vendor was probably responsible for the large amount of training required to develop the stimulus control, compared with the relative ease with which the same type of control had developed earlier with the single-column vendor. A more appropriate procedure with such a debilitated subject would have been to introduce gradually small differences in the size, shape, color, and location of the coin light

and coin slot while keeping the general function and pattern constant. Such a procedure would abstract the common features of coin slots and coin lights and make it possible for the child to respond appropriately to similar devices. The failure of the multiple fixed-ratio, variable-interval schedule to develop the normal performances characteristic of these schedules in the two stimuli also illustrates the child's minimal perceptual repertoire. Such failures of stimulus control are sometimes encountered in animals,[5] and may be corrected by special procedures such as reinforcement on the separate components of the schedule. No such corrective procedure was carried out. Furthermore, we do not know whether it would have been possible to develop the control by such corrective procedures or by trying again later in the experiment, after the subject had acquired other discriminative repertoires.

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It cannot be assumed that performances developed in the experimental room will have general effects elsewhere. The performances of these children, as with most organisms, come under the control of the particular situations in which they are reinforced. The performances in the experimental room probably are under very close control of the room itself and are unavailable to the child elsewhere. Even if the behavioral repertoire developed in the experiment had general effects on the child elsewhere, we could not expect the development of normal social behavior unless some kind of social repertoire which could be strengthened were already present. If such social behavior is altogether lacking, there is no chance for any inductive strengthening of it. It still may be possible, however, to develop social behavior outside of the experimental room. Social reinforcers would be used instead of candy, and social responses reinforced instead of key presses. The general plan in developing social behavior would be to manipulate social reinforcers (consequences of the child's performances supplied by other individuals), with the use of the same general principles applied in the artificial environment.

In general, tantrums and atavistic responses appeared less frequently during the latter parts of the experiment, suggesting that these tantrums, at least in part, are socially maintained. Programs of reinforcements were not changed too swiftly because of the possibility of anxiety attacks, temper tantrums, or breakdown of newly formed patterns of behavior following too abrupt procedural changes. The procedure of keeping social influences out of the experimental room may have weakened the tantrums by nonreinforcement. The development of a strong repertoire in the experimental room may have been another possible factor in the reduction in atavistic behavior. The large disposition to operate the devices in the experimental room may have simply displaced the tantrums by prepotency, as with Lindsley's psychotic adults who showed no psychotic performances while under the control of the fixed-ratio schedule of reinforcement.

Much of the schizophrenic's behavior exemplifies very weak performances which appear strong simply because most of the normally maintained behavior is weak. Lindsley[7] showed that during fixed-ratio reinforcement, the bizarre behavior of chronic schizophrenic adults appeared only during the pauses after reinforcement. Once the patient began responding appropriately to the schedule of reinforcement, the relatively strong behavior maintained by the candy and

cigarette reinforcements was prepotent over bizarre performances and other psychosis-like behavior. An example in the present experiment is Subject 1's scraping of the Plexiglas. This possibly occurred after he had deposited most of the coins in inoperative coin slots because his experimental performance became weak after the frequency of reinforcement became very low. If this analysis is correct, then the actual form of the behavior observed in psychotic patients is much less important than the absolute amount of behavior and, particularly, the levels of activity controlled by an effect on a social or socially derived environment. An analogous situation occurs frequently in normal individuals when they are placed in situations in which few of their currently available performances are relevant. Some examples are: experiments on sensory deprivation; waiting for someone to keep an appointment in a relatively isolated place; attending a formal meeting where the speaker's activity is not sufficiently important to the listener, but where at the same time, no behavior other than listening is appropriate. Under these circumstances, many individuals emit performances that are very similar to those of psychotic persons, such as rubbing the table constantly, scratching a particular part of the body, doodling, or some kind of oral activity. All of these activities have the common feature of not being supported by the external environment, particularly the social environment.



This experimental program is not viewed as an attempt at carrying out psychotherapy, but rather as an attempt to demonstrate what kinds of performances could be brought under the control of a specifiable environment with known behavioral processes. To the extent that variables manipulated in the experiment control the child's performances through normal behavioral processes, the child has advanced somewhat toward rehabilitation. Actual rehabilitation, however, would have to be carried out through the manipulation of social contingencies and the development of performances with which the child would interact with other individuals.

The results of these experiments show that the behavioral processes which have been studied are intact in both children, except for the multiple-schedule performance, which did not develop. This low over-all level of the performance, compared with the normal, is reminiscent of some kinds of brain damage which do not affect a performance except in its frequency of occurrence. The behavioral and physiologic histories are confounded in the present experiment, however. The facts are consistent with the hypothesis that these children underwent experiences that produced a very large deficit in behavior. Their repertoires actually may be inadequate because of deficits in performance rather than temporary suppressions by some debilitating mechanism, either physiologic or functional. These children may represent individuals in whom normal performances have never developed because the normal development of their repertoires was temporarily arrested at some time. Such a deficit might occur because the repertoire of the child is weakened through the normal behavioral processes by which behavior can be suppressed or eliminated. All of the basic processes by which new performances are generated, strengthened, maintained, eliminated, punished, suppressed, or controlled by special aspects of the environment are relevant to an analysis of how a particular history could produce a weak,

positively maintained repertoire. Some of these conditions have been tentatively outlined.[4,9] When conditions exist that severely weaken the existing repertoire of a child for any period of time, the performance becomes progressively more difficult to reinstate. The reason for this is that the environment of the now older child will not support the level of behavior of which he is capable, although this environment would support his level if the child were younger.

SUMMARY

Performances of two autistic children were recorded in an experimental environment consisting of vending machines delivering food and candy, a trained pigeon, a phonograph, a color kaleidoscope, and a pinball machine. These devices were operated either by keys mounted on them or by coins. Coins were delivered on various schedules when the children operated another key. Performances could be sustained on the coin key for 90-minute experimental sessions to demonstrate the normal effect of two schedules of reinforcement, to develop the coin as a generalized reinforcer, and to control the children's performances by the presence or absence of stimuli correlated with reinforcement or nonreinforcement.

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# Therapeutics

## THE DETERMINATION OF THE NUMBER OF PATIENTS REQUIRED IN A PRELIMINARY AND A FOLLOW-UP TRIAL OF A NEW CHEMOTHERAPEUTIC AGENT

EDMUND A. GEHAN, PH.D.
BETHESDA, MD.

*From the Biometrics Section, Cancer Chemotherapy National Service Center, National Institutes of Health*

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THE preliminary trial of a new drug in patients is fraught with many difficulties, most of which are medical. Some important factors to consider at the start of a trial are: the dose and route of administration of the drug, the dose schedule, and the type of patient. These are not the only considerations, however. It is important that the drug be given definitive trial, if effective, or put back on the shelf, if inefiective. Consequently, a preliminary trial should be conducted in such a manner that the probabilities of receiving further trial and being put back on the shelf are controlled to some degree for various true levels of effectiveness of the agent.

The concern here is with the determination of the number of patients to be used in a preliminary trial and the number of patients for a follow-up trial. The diagram in Fig. 1 shows the place of a preliminary and follow-up study in the clinical trial of a new agent. The number of patients to be placed in experimental and control groups for a comparative study is given by Kramer and Greenhouse.[1] A prior estimate of the effectiveness of the control agent and the improvement in effectiveness desired for the new agent is required.

The sample numbers for the preliminary and follow-up trials have been determined according to a sampling method known as double sampling,[2] where the initial sample is calculated to meet the probability specifications mentioned above. Since the purpose of the first sample is to decide whether the drug is worth studying further, the results given will be most applicable in a disease where almost all drugs are ineffective, such as in some types of cancer. Consequently, one would like to reject ineffective drugs as quickly as possible and push on to definitive trial those drugs with some degree of effectiveness.

No control group is suggested at this stage of the trial of the agent. If a comparative study were set up to look for small differences in effectiveness between the new agent and a control compound, it would require a very large number of patients. As an example, if one were searching for an agent that was 10 per cent more effective than a standard agent of 5 per cent effectiveness,

it would require 191 patients on each treatment (the probabilities of a false positive and false negative would be .05 and .10, respectively). Such a method of testing new agents would be expensive in patient material, time, and effort. It should be established by a preliminary and follow-up trial that a comparative trial is worth conducting.

It is assumed that the preliminary trial is to be conducted in a specified group of patients according to a particular drug regimen and the purpose of the study is to choose between:

Decision I: Drug is unlikely to be effective in x per cent of patients or more.
Decision II: Drug could be effective in x per cent of patients or more.

It should be emphasized that strictly speaking "the drug" is not being tested. The test is of the effectiveness of the drug *when administered in a particular manner to a certain type of patient.*

If the purpose of the study can be spelled out as above, it can be accomplished with a relatively small number of patients. The sample numbers given will *not* apply to the very early trial of a drug where a number of regimens are given to several types of patients in search of one that is not overly toxic and where one is willing to look for therapeutic effect. It is assumed that the drug regimen and type of patient have been chosen by preliminary experimentation (this may take a very substantial number of patients).

Suppose that the possible decisions for a particular trial are:

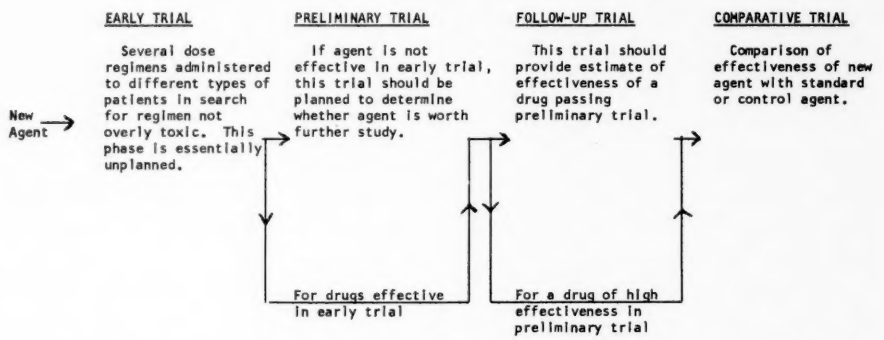
Decision I: Drug is unlikely to be effective in 20 per cent of patients or more.
Decision II: Drug could be effective in 20 per cent of patients or more.

Let us calculate the chance of consecutive treatment failures by number of patients, assuming that the true effectiveness of the drug is 20 per cent:

| CONSECUTIVE PATIENTS | CHANCE OF TREATMENT FAILURE IN GIVEN CONSECUTIVE NUMBER OF PATIENTS |
|---|---|
| 1 | .8 |
| 2 | $.8 \times .8 = .64$ |
| 3 | $.8 \times .8 \times .8 = .512$ |
| . | . |
| . | . |
| . | . |
| 8 | .168 |
| . | . |
| . | . |
| . | . |
| 11 | .086 |
| . | . |
| . | . |
| . | . |
| 14 | .044 |

If the drug were 20 per cent effective or more, there would be more than a 95 per cent chance that one or more successes would be obtained in 14 consecutive cases. Thus, if one observed 14 consecutive failures, the first decision would be made. The chance of having rejected a drug of 20 per cent effectiveness or more is less than 5 per cent.

FIGURE I.— THE SEQUENCE OF CLINICAL TRIALS FOR A NEW AGENT


EARLY TRIAL
Several dose regimens administered to different types of patients in search for regimen not overly toxic. This phase is essentially unplanned.
PRELIMINARY TRIAL
If agent is not effective in early trial, this trial should be planned to determine whether agent is worth further study.
FOLLOW-UP TRIAL
This trial should provide estimate of effectiveness of a drug passing preliminary trial.
COMPARATIVE TRIAL
Comparison of effectiveness of new agent with standard or control agent.
New Agent
For drugs effective in early trial
For a drug of high effectiveness in preliminary trial

Suppose a study with 14 patients was conducted. We would make observations on these patients and decide on a rule for proceeding. Such a rule might take the following form:

| TREATMENT SUCCESSES | ACTION |
|---|---|
| 0 | Drop drug |
| 1 | Include more patients in |
| . | |
| . | study to pinpoint |
| . | |
| 14 | effectiveness |

The number of additional patients can be determined so that the true effectiveness of the drug is estimated with given precision, i.e., standard error.

Table I provides the sample sizes necessary to decide whether an agent is not likely to be of a given true therapeutic effectiveness or is worthy of further trial at given levels of rejection error. (Rejection error ($\beta$) = chance of failing to send an agent to further trial, when it should have been.)

TABLE I. SAMPLE SIZE ($n_1$) REQUIRED FOR PRELIMINARY TRIAL OF A NEW AGENT FOR GIVEN LEVELS OF THERAPEUTIC EFFECTIVENESS AND REJECTION ERROR

| REJECTION ERROR ($\beta$) | THERAPEUTIC EFFECTIVENESS (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 |
| 5% | 59 | 29 | 19 | 14 | 11 | 9 | 7 | 6 | 6 | 5 |
| 10% | 45 | 22 | 15 | 11 | 9 | 7 | 6 | 5 | 4 | 4 |

Thus, if one is interested in an agent of 20 per cent effectiveness and is willing to accept a 10 per cent rejection error, a sample of 11 patients is necessary. If all 11 fail to respond, the agent is dropped. If one or more treatment successes are seen, the agent receives further trial.

Table II provides the number of additional patients ($n_2$) to be studied to estimate the true therapeutic effectiveness with a specified precision (approximately). The standard error of the estimated percentage of treatment successes after the first sample of $n_1$ patients is:

$$\text{Standard error} = \sqrt{\frac{p\ (100\text{-}p)}{n_1}}$$

where $p$ = percentage of treatment successes in the first sample,
$n_1$ = size of the first sample.

If the percentage of successes is approximately the same for future patients, the standard error with the total number of patients is about

$$\sqrt{\frac{p\ (100\text{-}p)}{N}} \qquad (1)$$

where $N = n_1 + n_2$ and p is the same as above. The second sample number, $n_2$, can then be determined so that approximately the required precision will result. Such a calculation is quite dependent upon p being near the true percentage of treatment successes. Since the sample number in the preliminary trial might be quite small, this may be too much to hope for. A more conservative value of p to substitute in equation (1) would be the upper 75 per cent confidence limit for the true percentage of treatment successes as derived from the first sample. This upper limit has been calculated and substituted for p in equation (1). Table II gives the sample numbers, $n_2$, so that approximately the required precision will be obtained in the estimate of the true percentage of treatment successes.*

Thus, if a sample of 11 patients had been taken in a preliminary trial (with a 10 per cent rejection error) in a search for an agent of 20 per cent effectiveness, and one treatment success was observed, then 60 additional patients would be required to guarantee an estimate of the true percentage effectiveness of the agent with a standard error of about 5 per cent. If the required standard error was about 10 per cent, then 7 additional patients would be needed.

Of course, there are many different ways of specifying a first and second sample. These double sampling plans require a single treatment success before the second sample is taken. Perhaps this number should be two or more for plans where the initial sample is large. The size of the second sample might be determined so that the final estimate of therapeutic effectiveness has a certain relative standard error, lower estimates of effectiveness having more precision

*"There is an approximation in applying ordinary methods of analysis to the results of a sequential experiment, but this is unlikely to be important."[2]

TABLE II. NUMBER OF ADDITIONAL PATIENTS ($n_2$) REQUIRED IN A FOLLOW-UP TRIAL TO ESTIMATE THE THERAPEUTIC EFFECTIVENESS OF AN AGENT WITH SPECIFIED PRECISION (STANDARD ERROR)

| REJECTION ERROR OF PRELIMINARY TRIAL | REQUIRED STANDARD ERROR | NO. OF TREATMENT SUCCESSES IN PRELIMINARY TRIAL | THERAPEUTIC EFFECTIVENESS (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 20 | 25 | 30 |
| 5% | NO. OF PATIENTS IN PRELIMINARY TRIAL | | 59 | 29 | 19 | 14 | 11 | 9 |
| | 5% | 1 | 0 | 4 | 30 | 45 | 60 | 70 |
| | | 2 | 0 | 17 | 45 | 63 | 78 | 87 |
| | | 3 | 0 | 28 | 58 | 76 | 87 | 91 |
| | | 4 | 0 | 38 | 67 | 83 | 89 | 91 |
| | | 5 | 0 | 46 | 75 | 86 | 89 | 91 |
| | 10% | 1 | 0 | 0 | 0 | 1 | 7 | 11 |
| | | 2 | 0 | 0 | 0 | 6 | 12 | 15 |
| | | 3 | 0 | 0 | 1 | 9 | 14 | 16 |
| | | 4 | 0 | 0 | 3 | 11 | 14 | 16 |
| | | 5 | 0 | 0 | 5 | 11 | 14 | 16 |
| 10% | NO. OF PATIENTS IN PRELIMINARY TRIAL | | 45 | 22 | 15 | 11 | 9 | 7 |
| | 5% | 1 | 0 | 21 | 42 | 60 | 70 | 83 |
| | | 2 | 0 | 35 | 60 | 78 | 87 | 93 |
| | | 3 | 0 | 47 | 72 | 87 | 91 | 93 |
| | | 4 | 4 | 57 | 81 | 89 | 91 | 93 |
| | | 5 | 9 | 65 | 85 | 89 | 91 | 93 |
| | 10% | 1 | 0 | 0 | 0 | 7 | 11 | 16 |
| | | 2 | 0 | 0 | 4 | 12 | 15 | 18 |
| | | 3 | 0 | 0 | 7 | 14 | 16 | 18 |
| | | 4 | 0 | 0 | 9 | 14 | 16 | 18 |
| | | 5 | 0 | 0 | 10 | 14 | 16 | 18 |

than higher estimates. To some extent, whatever choice is made is arbitrary and the way the plan works depends upon the unknown distribution of percentage effectiveness among the compounds that will be screened. The sampling plans specified here are designed to reject completely ineffective drugs quickly and send on to further trial those that possess some degree of effectiveness.

The sampling numbers given in Table I are the minimum numbers of patients that can be taken in the sample before a drug is dropped with a given chance of a rejection error. One might well ask how such a procedure would work on agents of different true percentage effectiveness than that specified as being of interest.

Table III presents the probabilities of sending drugs on to further trial for various levels of given true therapeutic effectiveness if the initial sample is taken according to the conditions specified for Table I.

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Note that the probability of sending a drug on to further trial is very high when the agent's true effectiveness is at or above the therapeutic effectiveness specified. However, the probability of sending a drug on to further trial is also substantial for agents of much less effectiveness than that searched for. For example, if an agent has a true effectiveness of 5 per cent, when we specify an effectiveness of 20 per cent as being of interest, the probability of further trial for this agent is .51. According to the usual statistical practice, this would be considered an "acceptance error" (and quite a high one), since we are doing further work on an agent of supposedly no interest. However, one might consider the reasoning of a physician when he specifies the therapeutic effectiveness that is of interest. The usual statement to the consulting statistician is that the agent is of interest "if it's effective at all." The statistician then points out that such a trial is impossible to plan, but that if a drug of 1 per cent effectiveness is being looked for, it will require a very large number of patients. The physician states that this number is impossible and then revises his original statement to something like the following: "I am interested in a new drug if it can provide definite benefit to one patient in five or more." The statistician then has something to work with and might specify an initial sample of 11 or 14 patients as given in Table I. The point is that the physician might not be at all unhappy if his sampling plan should have a high probability of sending on to further trial a drug of 5 per cent effectiveness. Consequently, the probabilities given in Table III have to be evaluated with full knowledge of the disease in which the drug is to be tried. If it is a disease where no agent of any real effectiveness exists and where it might be expected that nearly all agents will be completely ineffective, it might be quite reasonable to proceed in the large-scale testing of chemotherapeutic agents according to one of the double sampling plans outlined.

The definition of "therapeutic effectiveness" is a medical problem that is an important part of any of these sampling plans (or any other plans, for that matter). In diseases where drugs have been completely ineffective up to now, the definition may pose no serious difficulties and any objective benefit to the patient might qualify as "therapeutic effect." In diseases where transient regressions or partial benefits are observed with presently available drugs, it would seem reasonable to define a "therapeutic effect" as a marked objective improvement in the patient's

TABLE III. THE PROBABILITY OF A SECOND SAMPLE FOR AGENTS OF GIVEN TRUE THERAPEUTIC EFFECTIVENESS WHEN THE INITIAL SAMPLE IS SPECIFIED AS IN TABLE I

| REJECTION ERROR IN PRELIMINARY TRIAL | THERAPEUTIC EFFECTIVENESS TESTED | TRUE THERAPEUTIC EFFECTIVENESS (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 3 | 5 | 10 | 20 | 30 | 40 | 50 |
| 5% | 5% $n_1 = 59$ | .45 | .83 | .95 | .998 | .999 | .999 | .999 | .999 |
| | 10% $n_1 = 29$ | .25 | .59 | .77 | .95 | .998 | .999 | .999 | .999 |
| | 20% $n_1 = 14$ | .13 | .35 | .51 | .77 | .96 | .993 | .999 | .999 |
| | 30% $n_1 = 9$ | .09 | .24 | .37 | .61 | .87 | .96 | .99 | .998 |
| | 40% $n_1 = 6$ | .06 | .17 | .26 | .47 | .74 | .88 | .95 | .98 |
| | 50% $n_1 = 5$ | .05 | .14 | .23 | .41 | .67 | .83 | .92 | .97 |
| 10% | 5% $n_1 = 45$ | .37 | .75 | .90 | .99 | .999 | .999 | .999 | .999 |
| | 10% $n_1 = 22$ | .20 | .49 | .68 | .90 | .99 | .999 | .999 | .999 |
| | 20% $n_1 = 11$ | .10 | .28 | .43 | .69 | .91 | .98 | .996 | .999 |
| | 30% $n_1 = 7$ | .07 | .19 | .30 | .52 | .79 | .92 | .97 | .992 |
| | 40% $n_1 = 5$ | .05 | .14 | .23 | .41 | .67 | .83 | .92 | .97 |
| | 50% $n_1 = 4$ | .04 | .11 | .19 | .34 | .59 | .76 | .87 | .94 |

disease. This would prevent so-called biologic variations in the disease or minor benefits to the patient from being classed as treatment successes. In diseases where agents of a high degree of effectiveness exist, it would appear that the sampling plans would not be very useful until the patient had relapsed after administration of the known agents or was resistant to these agents.

SUMMARY

Double sampling plans have been used to determine sample sizes for the conduct of a preliminary and a follow-up trial of a new drug. The initial sample is determined so that, if all the patients do not respond, the drug will be dropped with a known chance of a rejection error. If one or more of the patients in the first sample respond, the size of the second sample is determined so that the true effectiveness of the drug is estimated with approximately a specified precision, as defined by the standard error. The probabilities of having a second sample are calculated for drugs with the assumption of various true percentages of effectiveness. Some discussion is given of where such sampling plans might be useful.

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# Infectious Diseases

## STUDIES OF THE EPIDEMIOLOGY OF STAPHYLOCOCCAL INFECTION

### I. Infection in Hospitalized Patients

B. HARVEY MINCHEW, M.D.,* AND LEIGHTON E. CLUFF, M.D.**

SEATTLE, WASH., AND BALTIMORE, MD.

*From the Department of Medicine, Division of Infectious Disease and Allergy, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital*

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THE rapid development of interest in staphylococcal infections occurring in hospitals has exceeded the knowledge available on the epidemiology and pathogenesis of this type of infection. Practically all epidemiologic studies of this subject have been concerned with epidemics and very little is known of the incidence of staphylococcal infections in hospitals during nonepidemic periods.

It has long been thought that the varying susceptibility of persons to these infections is attributable to certain associated illnesses, such as diabetes mellitus, neoplastic disease, skin disease, and to differences in age, as illustrated by epidemics which have occurred among newborn infants, but few data have been available to support or refute these opinions.

The objectives of this study have been threefold:

1. To determine the incidence of staphylococcal infection acquired in The Johns Hopkins Hospital.

2. To define and characterize the types of patients who develop these infections.

3. To identify the bacteriophage types of staphylococci producing the hospital-acquired infections.

This report is based on investigations during 1959.

#### METHODS

The Johns Hopkins Hospital is a 1,077 bed general hospital (including 66 bassinets) with private, semiprivate, and public services. The hospital rooms

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*Senior Assistant Surgeon (R), Member, Epidemic Intelligence Service, Communicable Disease Center, United States Public Health Service, United States Department of Health, Education and Welfare, assigned to The Johns Hopkins University School of Medicine. Present address: Assistant Resident Physician, Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

**Associate Professor of Medicine, The Johns Hopkins University School of Medicine.

are designed for occupancy by one, two, or four patients, and there are several "open" wards on each service. There are three separate operating suites: the general operating room serving the entire hospital; the operating suite for obstetric and gynecologic surgery; and a suite for ophthalmologic surgery. These three operating room areas are located in different buildings and staffed by different personnel.

Two systems were used to detect patients with staphylococcal infections acquired in the hospital. By the first method, each patient admitted to the hospital had attached to his chart a "report-of-infection" card. This card was 5½ by 5½ inches, colored bright pink, and had the patient's name, ward, admission date, history number, physician, age, race, and sex stamped in the upper right-hand corner. If a patient developed an infection while in the hospital, the physician checked the appropriate space on the card and indicated what type of infection was present (i.e., boil, postoperative wound, etc.) and the results of bacterial cultures if available. The card was sent to the Committee on Infections in the Hospital. If a patient did not develop an infection while in the hospital, this was noted on the "report-of-infection" card when the patient was discharged from the hospital. This system required a card to be completed for each patient in the hospital, thus assuring, as well as possible, completeness of reporting. The second method of case finding involved tabulating the names of patients from whom staphylococci were isolated in the hospital bacteriology laboratory. Each patient, reported by the "report-of-infection" card and/or by the bacteriology laboratory, was visited and his or her chart reviewed. Patients were examined when there was insufficient information in the chart. At the time each patient was visited additional information was recorded on marginal keypunch cards.

In addition to the above methods of case finding, follow-up home visits were made to a sample group of newborn infants over a period of 2 to 6 weeks after discharge from the hospital.

Staphylococcal infection acquired in the hospital was defined as: (1) infection manifesting itself after admission to, but before discharge from, the hospital; (2) infection in a newborn infant within 30 days of discharge from the hospital; (3) breast infection in a nursing mother within 45 days after discharge from the hospital; and (4) postoperative wound infection within 7 days after discharge from the hospital. As there is no routine follow-up of discharged operative patients, this group included only a few individuals who were readmitted because of their infections. The presence of inflammation or purulent discharge and the isolation of a pure or predominant growth of staphylococci on culture characterized the staphylococcal infection in all of the patients.

The primary isolation of staphylococci from clinical specimens was made in the hospital bacteriology laboratory. During the first 3 months of the study, staphylococci were examined after subculture on tellurite-glycine agar,[1] but subsequently the coagulase-mannitol test[2,3] was used. Those strains that were either tellurite or coagulase positive were typed with the bacteriophage technique described by Blair.[4] The bacteriophage typing was done at a routine test dilution only. Susceptibility to various antibiotics was determined by the "disc" method and any strain not showing a zone of inhibition was considered resistant.

RESULTS

Two hundred and thirty-four patients acquired a staphylococcal infection in the hospital as shown in Table I. Of the patients infected, 70.5 per cent had developed the infection postoperatively. During the same period of time only 40 per cent of the patients in the hospital were operated upon; therefore, a disproportionately high percentage of the infections occurred in operative patients.

Fig. 1 illustrates the monthly variation in frequency of hospital-acquired staphylococcal infections calculated on the basis of the number of infections per 10,000 patient days. This hospital averages from 20,000 to 25,000 patient days every month; therefore, it can be seen that 12 to 32 infections occurred each month. The decrease in number of infections after February was apparent. Unfortunately, for technical reasons, data were not available for March and April.

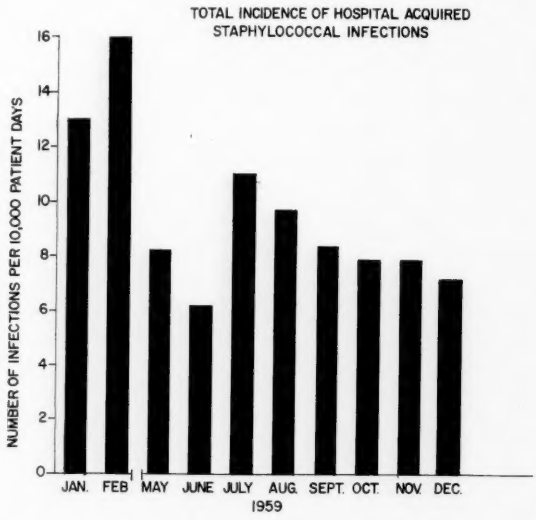


Fig. 1.—The over-all incidence of staphylococcus infection acquired by hospitalized patients during 1959, showing a decrease in frequency of infection after February.

That the decline in the over-all incidence of infection did not occur equally throughout the hospital is demonstrated in Fig. 2. Here it is seen that there was a decrease in the frequency of postoperative wound infections between February and May, but no appreciable change was seen on the medical or pediatric service. "Patients at risk" was defined as the number of patients discharged from the service during the month in addition to the number of patients on the service the last day of the month. Tabulation of the data using "patient days" as the denominator gave comparable results, as has also been found by others.[14]

In a survey of the over-all incidence of infection in the hospital, rather marked variations in infection rates on specific services within the hospital are masked. For example, in September, 5 postoperative wound infections developed on the neurological surgery service, and, although this was a definite increase in rate of infection on that service, it is not reflected in the data shown in Fig. 1.

*Infection in Newborn Infants and Postpartum Women.*—The data presented in Table I indicate that infections of newborn infants and postpartum women were relatively uncommon during the time of the surveillance. There was an average of 266 deliveries per month, and only 10 infections among either the newborn infants or the mothers were reported or detected during the year. Of these ten, 7 occurred in infants and 3 in nursing mothers. The infected infants and the infected mothers were not related. Of the 7 infections in newborn infants, 6 occurred in premature babies. Three of these 6 occurred in January, one in May, and 2 in October. The seventh infected infant was in another nursery unit and the staphylococcus involved was nontypable.

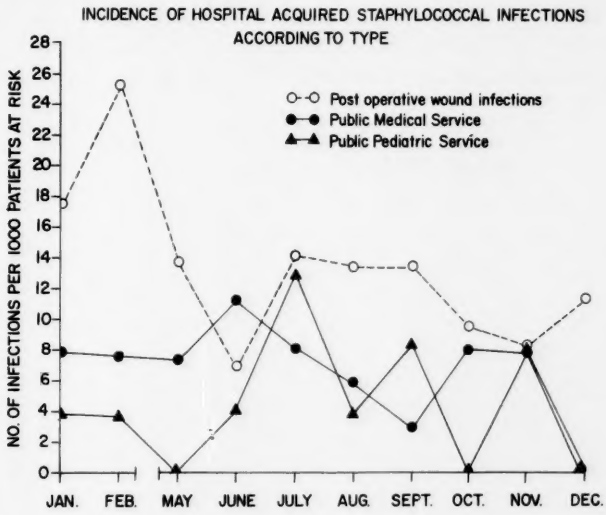


Fig. 2.—The incidence of staphylococcal infection acquired by patients hospitalized on the surgical, medical, and pediatric services of the hospital during 1959, showing a decline in frequency of infection after February only on the surgical service.

TABLE I. HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS

| TYPE OF INFECTIONS | NO. OF INFECTIONS | NO. OF PATIENTS |
|---|---|---|
| Neonatal and postpartum | 10 | 10 (4.3%) |
| Post operative wounds | 167 | 165 (70.5%) |
| Others | 59 | 59 (25.2%) |
| Total | 236 | 234 (100.0%) |

Epidemiologic studies performed in the premature nursery in January revealed two nasal carriers of the 80/81 staphylococcus among the personnel. Both of these persons were removed from the premature nursery and no other carriers of the 80/81 staphylococcus have been permitted to work there. However, there

have been 3 infants infected since that time, two of whom were infected with the 80/81 strain.

Four of the infants had superficial skin infection, 2 had purulent conjunctivitis, and one had purulent rhinitis. Two of the mothers had breast abscesses and one had furuncles on her breast. There were no infections described in the infants of the infected mothers.

The infected infants ranged from 5 to 21 days of age with a mean age of 11.3 days.

*Infections Other Than Neonatal, Postpartum, or Postoperative Wound Infections.*—The types of infections grouped under this heading are presented in Table II. It is worthy of note that the second most common type of infection in these patients was bacteremia. The patients developing these infections were located in all parts of the hospital, but the majority of them (63 per cent) occurred in medical and pediatric patients.

TABLE II. TYPES OF HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS OTHER THAN POSTOPERATIVE WOUNDS, NEONATAL, OR POSTPARTUM

| INFECTION | NO. OF CASES | |
|---|---|---|
| Furunculosis | 15 | |
| Bacteremia | 13 | |
| Underlying cause: | | |
| Uncertain | | 5 |
| Intravenous catheter | | 3 |
| Abscess | | 2 |
| Meningitis | | 1 |
| Urinary tract | | 1 |
| Thrombophlebitis | | 1 |
| Abscess | 9 | |
| Urinary tract | 4 | |
| Infected burn | 3 | |
| Pneumonia | 2 | |
| Infected intravenous cut-down site | 2 | |
| Infected biopsy site | 2 | |
| Infected decubitus | 1 | |
| Blepharitis | 1 | |
| Infected dermatitis | 1 | |
| Conjunctivitis | 1 | |
| Enterocolitis | 1 | |
| Paronychia | 1 | |
| Cellulitis | 1 | |
| Otitis media | 1 | |
| Endometritis | 1 | |
| Total | 59 | |

Table III presents the frequency distribution of these patients by age, race, and sex and indicates that the greatest number of infections was seen in persons under 9 years of age and persons between 60 and 69 years of age. The highest percentage of patients who acquired infection (32 per cent) was in the category of white males. It was not possible, for technical reasons, to calculate "attack rates" for some of these data, but attempts are now being made to better define these parameters of infection.

Table IV presents the "attack rates" for patients on the public medical service by race and sex and indicates that there was no marked difference in these rates for adult medical patients. In Table V the attack rates of adult medical patients according to age are given, and while the actual rates were not impressively different there is a trend suggesting an increased rate with increasing age.

TABLE III. AGE AND SEX DISTRIBUTION OF PATIENTS WITH HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS OTHER THAN POSTOPERATIVE WOUNDS, NEONATAL, OR POSTPARTUM

| AGE | WHITE MALES | NEGRO MALES | WHITE FEMALES | NEGRO FEMALES | TOTALS | |
|---|---|---|---|---|---|---|
| | | | | | NO. | % |
| 0– 9 | 4 | 3 | 3 | 2 | 12 | 20.3 |
| 10–19 | 1 | 0 | 0 | 1 | 2 | 3.4 |
| 20–29 | 2 | 0 | 1 | 2 | 5 | 8.4 |
| 30–39 | 1 | 2 | 1 | 2 | 6 | 10.2 |
| 40–49 | 2 | 2 | 2 | 2 | 8 | 13.5 |
| 50–59 | 5 | 2 | 3 | 0 | 10 | 16.9 |
| 60–69 | 4 | 2 | 1 | 7 | 14 | 23.7 |
| 70–79 | 0 | 1 | 0 | 0 | 1 | 1.7 |
| 80–89 | 0 | 0 | 1 | 0 | 1 | 1.7 |
| 90–99 | 0 | 0 | 0 | 0 | 0 | |
| Total | 19(32.2%) | 12(20.3%) | 12(20.3%) | 16(27.1%) | 59 | 100 |
| Mean age | 40 | 40 | 40 | 43 | 40.7 | |

The primary diagnoses in patients developing these infections were quite varied as shown in Table VI. Cancer was present in 17 per cent of the patients. To determine actual attack rates of patients with certain diseases, an attempt was made to obtain data on the number with specific diagnoses who were admitted to the public medical service during the study period. The only source of such information is a "Resident's Book" in which the assistant residents on each ward list the primary diagnoses for all patients admitted. Such information is subject to error because of omissions; however, the attack rates for patients with six different diagnoses are presented in Table VII. These figures suggest that patients with dermatitis, lupus erythematosus, and cirrhosis were more susceptible to staphylococcal infection than were patients with cancer, diabetes mellitus, or hypertension. It is equally interesting that there was no apparent difference in the rates for persons with diabetes mellitus or cancer when compared to patients with hypertension.

As indicated in Table II, except for the patients with bacteremia, pneumonia, and enterocolitis, most of the infections were not serious. Of 25 adult medical patients with staphylococcal infection, however, 2 (8 per cent) died as a direct consequence of the infection (Table VIII). The importance of the infection as a cause of death was determined by autopsy reports when available or by the clinician's "death note" if no autopsy was performed. The seriousness of the underlying disease in these patients is emphasized by the fact that at least 16 per cent died from a cause apparently unrelated to the staphylococcal infection.

TABLE IV. ATTACK RATES BY RACE AND SEX FOR PUBLIC MEDICAL PATIENTS WITH HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS OTHER THAN POSTOPERATIVE WOUND, NEONATAL, AND POSTPARTUM

| RACE AND SEX | NO. OF INFECTIONS | ESTIMATED NO. OF DISCHARGES* | ATTACK RATES (%) |
|---|---|---|---|
| White males | 3 | 596 | 0.5 |
| Negro males | 7 | 648 | 1.0 |
| White females | 6 | 456 | 1.3 |
| Negro females | 10 | 601 | 1.6 |
| Total | 26 | 2,301 | 1.1 |

*Using 4 months in 1959 and 6 corresponding months in 1958.

TABLE V. ATTACK RATES BY AGE FOR PUBLIC MEDICAL PATIENTS WITH HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS OTHER THAN POSTOPERATIVE WOUNDS, NEONATAL, OR POSTPARTUM

| AGE | NO. OF INFECTIONS | ESTIMATED NO. OF DISCHARGES* | ATTACK RATES |
|---|---|---|---|
| 0– 9 | 0 | 2 | 0 |
| 10–19 | 1 | 126 | 0.8 |
| 20–29 | 1 | 238 | 0.4 |
| 30–39 | 2 | 351 | 0.6 |
| 40–49 | 7 | 489 | 1.4 |
| 50–59 | 5 | 431 | 1.2 |
| 60–69 | 5 | 356 | 1.4 |
| 70–79 | 4 | 243 | 1.6 |
| 80–89 | 1 | 56 | 1.8 |
| 90–99 | 0 | 9 | 0 |
| Total | 26 | 2,301 | 1.1 |

*Using 4 months in 1959 and 6 corresponding months in 1958.

*Infection of Postoperative Wounds.*—There were 165 persons who developed 167 postoperative staphylococcal wound infections during this study. The 2 patients who developed 2 wound infections each did so following entirely different procedures performed by different surgical services. Interestingly, the two infections of each patient were attributable to different bacteriophage types of staphylococci.

The frequency distribution of postoperative wound infections by age, race, and sex is presented in Table IX. It should be noted that only 6.6 per cent of these infections occurred in persons under 9 years of age, whereas 20 per cent of the infections other than postoperative, neonatal, or postpartum occurred in the same age group (Table III). This observation is more than a reflection of the frequency distribution of the ages of patients admitted to the hospital as will be pointed out subsequently.

The specific attack rates for the Surgical Service patients according to race and sex are shown in Table X and no impressive differences were observed.

TABLE VI. PRIMARY DIAGNOSIS IN PATIENTS WHO DEVELOPED "OTHER" HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS

| INFECTION | NO. OF CASES |
|---|---|
| Cancer | 10 |
| Diabetes mellitus | 4 |
| Diarrhea | 3 |
| Burns | 3 |
| Benign tumors | 3 |
| Cirrhosis | 3 |
| Antenatal pregnancy | 2 |
| Epilepsy | 2 |
| Congenital heart disease | 2 |
| Uncertain | 2 |
| Dermatitis | 2 |
| Tuberculosis | 1 |
| Hydrocephalus | 1 |
| Plumbism | 1 |
| Congenital kidney analomy | 1 |
| Hodgkin's disease | 1 |
| Cleft palate | 1 |
| Subarachnoid hemorrhage | 1 |
| Hemophilus meningitis | 1 |
| Diverticulitis | 1 |
| Benign prostatic hypertrophy | 1 |
| Bronchitis | 1 |
| Traumatic concussion | 1 |
| Sarcoidosis | 1 |
| Uremia | 1 |
| Lupus erythematosus | 1 |
| Dermatomyositis | 1 |
| Hyperthyroidism | 1 |
| Rheumatic heart disease | 1 |
| Pneumonia | 1 |
| Cerebrovascular accident | 1 |
| Congestive heart failure | 1 |
| Hypertension | 1 |
| Tetanus | 1 |
| Total | 59 |

Analysis of the wound infections in patients operated upon in the general operating room showed that the rate of infection varied with different wards in the hospital (Table XI). While both Halsted and Osler (Medical Service) are classified as mixed pay status, 63.9 per cent of the Halsted patients were ward patients as compared to 82.8 per cent for Osler. Comparison with these rates by the chi-square test reveals that the rate was significantly different, at the 5 per cent level or lower, only in Halsted, Marburg, and Harriet Lane (Pediatric Service). The differences in the other rates were statistically significant at a 5 per cent level of confidence.

Table XII presents the age specific attack rates for Halsted patients who developed postoperative staphylococcal wound infections. Again the same trend of increasing rate with increasing age was seen; however, there was a decrease in rate in the group 80 to 89 years of age. The significance of this must await the collection of additional data, since the group studied was small. Four of the 90 infections (4.4 per cent) occurred in persons under 9 years of age, whereas 18.6 per cent of the patients discharged from this service were in this age group.

TABLE VII. INCIDENCE OF HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS IN PUBLIC MEDICAL PATIENTS BY DIAGNOSES

| DIAGNOSIS | NO. OF INFECTIONS | NO. OF PATIENTS | ATTACK RATES (%) |
|---|---|---|---|
| Cancer | 4 | 163 | 2.4 |
| Diabetes mellitus | 3 | 92 | 3.2 |
| Hypertension | 2 | 67 | 2.9 |
| Hepatic cirrhosis | 3 | 38 | 7.8 |
| Dermatitis | 2 | 8 | 25.0 |
| Lupus erythematosus | 1 | 12 | 8.3 |

TABLE VIII. MORTALITY RATES IN 25 PUBLIC MEDICAL PATIENTS WITH HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS*

| | RELATED TO STAPH. | NOT DUE TO STAPH. | RELATION TO STAPH. UNKNOWN | TOTAL |
|---|---|---|---|---|
| No. who died | 2 | 4 | 3 | 9 |
| Mortality rate (%) | 8 | 16 | 12 | 36 |

*Of the 26 infections information not available on one.

The associated illnesses in patients with postoperative staphylococcal wound infections are given in Table XIII, and cancer was again seen to be the most common single underlying disease. For 6 of the diagnoses analyzed, it was possible to calculate specific attack rates, and these figures are presented in Table XIV. Patients with burns, cancer, and cholecystitis show the highest rates. The relatively high attack rate for patients with herniated nucleus pulposus is undoubtedly related to the epidemic which occurred on the neurological surgery service, as 2 of the 4 infections developed during the outbreak. The 53 diagnoses classified as "others" consisted of those which occurred only once (Table XIII).

Attack rates could be tabulated for certain types of operations, and these are presented in Table XV. The two highest rates were seen in patients undergoing radical neck dissections and amputations, both of which may reflect an underlying diagnosis of cancer.

The over-all postoperative infection rate was about 2.0 per cent (Tables XI and XII), but it is apparent from Table XV that this is no indication of the frequency with which postoperative wound infections are occurring in certain types of patients.

Attempts were made to determine whether the duration of an operation was an important predisposing factor in the development of a postoperative staphylococcal wound infection. The duration of 84 operations in which wound infection was detected and the duration of 1,264 operations of the same types which did not become infected were tabulated to the nearest 30-minute period and the data, as shown in Table XVI, failed to show any difference of note.

TABLE IX. AGE, RACE, AND SEX DISTRIBUTION OF PATIENTS WITH POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS

| AGE | WHITE MALES | NEGRO MALES | WHITE FEMALES | NEGRO FEMALES | TOTAL | % |
|---|---|---|---|---|---|---|
| 0– 9 | 3 | 2 | 2 | 4 | 11 | 6.6 |
| 10–19 | 4 | 2 | 4 | 1 | 11 | 6.6 |
| 20–29 | 2 | 3 | 4 | 3 | 12 | 7.2 |
| 30–39 | 7 | 3 | 8 | 8 | 26 | 15.7 |
| 40–49 | 8 | 6 | 8 | 10 | 32 | 19.4 |
| 50–59 | 14 | 2 | 7 | 10 | 33 | 20.0 |
| 60–69 | 11 | 4 | 8 | 0 | 23 | 13.9 |
| 70–79 | 8 | 2 | 3 | 1 | 14 | 8.4 |
| 80–89 | 2 | 0 | 1 | 0 | 3 | 1.8 |
| 90–99 | 0 | 0 | 0 | 0 | 0 | —— |
| Total | 59(35.8%) | 24(14.5%) | 45(27.2%) | 37(22.4%) | 165 | 100 |
| Mean age | 50 | 42 | 46 | 39 | 44 | |

TABLE X. ATTACK RATES OF POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS IN PUBLIC OPERATIVE PATIENTS BY RACE AND SEX

| | NO. OF INFECTIONS | ESTIMATED NO. OF DISCHARGES* | ATTACK RATES (%) |
|---|---|---|---|
| White males | 34 | 1,534 | 2.2 |
| Negro males | 15 | 789 | 1.9 |
| White females | 24 | 1,364 | 1.8 |
| Negro females | 17 | 768 | 2.2 |
| Total | 90 | 4,455 | 2.0 |

*Using 4 months in 1959 and 6 corresponding months in 1958.

The interval between operation and the recognition of postoperative wound infection is shown in Table XVII and suggests that the administration of prophylactic antibiotics prolonged this period.

Most of the postoperative wound infections were not severe, but bacteremia was detected in 4.8 per cent of the patients (Table XVIII). Detected bacteremia did not appear to be associated with any particular type of postoperative wound infection although 3 patients had had chest surgery.

The mortality rates in 80 Halsted patients with postoperative staphylococcal infection are shown in Table XIX. Ten per cent of these patients died as a result of their infection.

The influence of prophylactic antibiotics on the occurrence of antibiotic-resistant staphylococci in wound infections is illustrated in Table XX and shows that prophylactic antibiotics increased the likelihood that the infection was due to an antibiotic-resistant staphylococcus.

Table XXI shows the bacteriophage types of staphylococci responsible for the infections. The 80/81 staphylococcus was the commonest identifiable strain but was the cause of only 33.3 per cent of the infections. Nontypable and a

TABLE XI. INCIDENCE OF POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS BY BUILDING—GENERAL OPERATING ROOM, 1959

| BUILDING | PAY STATUS | NO. OF INFECTIONS | NO. OF OPERATIONS | ATTACK RATES (%) |
|---|---|---|---|---|
| Halsted (Surgery) | Mixed | 90 | 3,739 | 2.4 |
| Brady (Surgery) (Medicine) | Mixed | 21 | 1,226 | 1.7 |
| Marburg (Surgery) (Medicine) | Private | 9 | 948 | 0.9 |
| Thayer (Surgery) (Medicine) | Private | 4 | 333 | 1.2 |
| Osler (Medicine) | Mixed | 8 | 444 | 1.8 |
| Harriet Lane (Pediatrics) | Mixed | 6 | 561 | 1.0 |
| Total | | 138 | 7,251 | 1.9 |

TABLE XII. INCIDENCE OF POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS IN PUBLIC OPERATIVE PATIENTS BY AGE

| AGE | NO. OF INFECTIONS | ESTIMATED NO. OF DISCHARGES* | ATTACK RATES (%) |
|---|---|---|---|
| 0– 9 | 4 | 828 | 0.4 |
| 10–19 | 7 | 638 | 1.0 |
| 20–29 | 7 | 441 | 1.6 |
| 30–39 | 12 | 652 | 1.8 |
| 40–49 | 16 | 669 | 2.4 |
| 50–59 | 19 | 625 | 3.0 |
| 60–69 | 15 | 380 | 3.9 |
| 70–79 | 9 | 176 | 5.1 |
| 80–89 | 1 | 41 | 2.4 |
| 90–99 | 0 | 5 | 0.0 |
| Total | 90 | 4,455 | 2.0 |

*Using 4 months in 1959 and 6 corresponding months in 1958.

variety of other bacteriophage types of staphylococci produced most of the infections.

## DISCUSSION

The numerous reports of epidemics of staphylococcal disease in hospitals[5] attest the size of this problem. The variable epidemiologic patterns which staphylococcal diseases may follow are illustrated by the occurrence of epidemics in newborn nurseries,[6] postoperative wounds,[7,8] and adult medical patients.[9,10] Consequently, to prevent and to control these diseases it is necessary to have knowledge of the incidence of the infections among the various groups of patients in the hospital. The most effective way to obtain such information is with the

TABLE XIII. DIAGNOSES IN PATIENTS DEVELOPING POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS

| DIAGNOSIS | NO. | % |
|---|---|---|
| Cancer | 36 | 21.8 |
| Hernia | 9 | 5.4 |
| Cholecystitis or cholelithiasis | 9 | 5.4 |
| Uncertain | 9 | 5.4 |
| Benign prostatic hypertrophy | 7 | 4.2 |
| Burns | 6 | 3.6 |
| Herniated nucleus pulposus | 6 | 3.6 |
| Myomas of the uterus | 5 | 3.0 |
| Traumatic injuries | 6 | 3.6 |
| Diabetes mellitus | 4 | 2.4 |
| Congenital heart disease | 4 | 2.4 |
| Menorrhagia | 3 | 1.8 |
| Benign tumor | 3 | 1.8 |
| Fractured hip | 3 | 1.8 |
| Arterial occlusion | 2 | 1.2 |
| Others | 53 | 32.1 |
| Total | 165 | 100 |

TABLE XIV. INCIDENCE OF POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS ACCORDING TO DIAGNOSES

| DIAGNOSIS | NO. OPERATED UPON | NO. INFECTED | ATTACK RATES (%) |
|---|---|---|---|
| Burns | 53 | 6 | 11.3 |
| Cancer | 282 | 24 | 8.5 |
| Cholecystitis and/or cholelithiasis | 76 | 5 | 6.6 |
| Herniated nucleus pulposus | 74 | 4 | 5.4 |
| Congenital heart disease | 108 | 4 | 3.7 |
| Hernia | 284 | 7 | 2.5 |

TABLE XV. INCIDENCE OF POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS ACCORDING TO TYPE OF OPERATION

| TYPE OF OPERATION | NO. OF OPERATIONS | NO. INFECTED | ATTACK RATES (%) |
|---|---|---|---|
| Radical neck dissection | 36 | 4 | 11.1 |
| Amputations | 50 | 5 | 10.0 |
| Lobectomy (lung) | 13 | 1 | 7.7 |
| Bone grafts | 32 | 2 | 6.2 |
| Cholecystectomy | 83 | 5 | 6.0 |
| Cardiac surgery | 121 | 7 | 5.7 |
| Skin graft | 152 | 8 | 5.2 |
| Mastectomy | 60 | 3 | 5.0 |
| Hip prosthesis | 65 | 3 | 4.6 |
| Laminectomy | 23 | 1 | 4.3 |
| Exploration of Spine | 82 | 3 | 3.6 |
| Herniorrhaphy | 289 | 7 | 2.4 |
| Hysterectomies | 570 | 14 | 2.4 |
| Arterial grafts and endarterectomy | 71 | 1 | 1.4 |

TABLE XVI. DURATION OF OPERATIONS

| | TOTAL NO. | MEAN | MEDIAN |
|---|---|---|---|
| Wound infected | 84 | 156 minutes | 131 minutes |
| Not infected | 1,264 | 182 minutes | 96 minutes |

TABLE XVII. INTERVALS BETWEEN OPERATION AND RECOGNITION OF STAPHYLOCOCCAL WOUND INFECTION

| PROPHYLACTIC ANTIBIOTICS | MEAN | MEDIAN |
|---|---|---|
| No (83) | 8.4 days | 6 days |
| Yes (84) | 10.7 days | 8 days |

TABLE XVIII. INCIDENCE OF DETECTED BACTEREMIA IN PATIENTS WITH POSTOPERATIVE WOUND INFECTIONS

| OPERATION | NO. OF PATIENTS WITH BACTEREMIA | NO. OF PATIENTS WITH WOUND INFECTIONS |
|---|---|---|
| Hernia | 1 | 9 |
| Hysterectomy | 1 | 14 |
| Craniotomy | 1 | 1 |
| Hip nailing | 1 | 3 |
| Cardiac | 1 | 5 |
| Mediastinotomy | 1 | 1 |
| Prostatectomy | 1 | 6 |
| Resection of esophagus | 1 | 1 |
| Others | 0 | 125 |
| Total | 8(4.8%) | 165 |

TABLE XIX. MORTALITY RATES IN 80 PUBLIC WARD PATIENTS WITH POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS*

| | RELATED TO STAPH. | NOT DUE TO STAPH. | RELATION TO STAPH. UNKNOWN | TOTAL |
|---|---|---|---|---|
| No. who died | 8 | 0 | 4 | 12 |
| Mortality rates (%) | 10 | 0 | 5 | 15 |

*Of the 90 infections information not available on 10.

use of some type of reporting system. (The Epidemic Intelligence Service, Communicable Disease Center, United States Public Health Service, has available an outline of recommendations for establishing a reporting system.[11]) The adequacy of data obtained by a reporting system is directly dependent upon its completeness. During this study, we received a "report-of-infections" card on 93 per cent of the patients discharged from the hospital and 87.2 per cent of these cards were completed.

TABLE XX. DISTRIBUTION OF ANTIBIOTIC RESISTANCE (DISC) IN RELATION TO PROPHYLACTIC ANTIBIOTICS IN POSTOPERATIVE STAPHYLOCOCCAL WOUND INFECTIONS

| PROPHYLACTIC ANTIBIOTIC | NO. TESTED | | RESISTANT | | | |
|---|---|---|---|---|---|---|
| | | | NO. | | % | |
| | YES | NO | YES | NO | YES | NO |
| Tetracycline | 73 | 77 | 60 | 50 | 82.2 | 64.9 |
| Chloramphenicol | 69 | 74 | 21 | 17 | 30.4 | 22.9 |
| Streptomycin | 73 | 77 | 63 | 51 | 86.3 | 66.2 |
| Penicillin | 73 | 78 | 65 | 62 | 89.0 | 79.4 |
| Erythromycin | 73 | 75 | 33 | 19 | 45.2 | 25.3 |
| Novobiocin | 75 | 77 | 6 | 2 | 8.0 | 2.6 |

TABLE XXI. DISTRIBUTION OF BACTERIOPHAGE TYPES AMONG HOSPITAL-ACQUIRED STAPHYLOCOCCAL INFECTIONS

| | 80/81 | | NONTYPABLE | | OTHER | | TOTAL | |
|---|---|---|---|---|---|---|---|---|
| | NO. | % | NO. | % | NO. | % | NO. | % |
| Postoperative | 47 | 30.3 | 44 | 28.3 | 64 | 41.2 | 155 | 100 |
| Neonatal and postpartum | 5 | 55.6 | 2 | 22.2 | 2 | 22.2 | 9 | 100 |
| Other infections | 21 | 38.2 | 12 | 21.8 | 22 | 40.0 | 55 | 100 |
| Total | 73 | 33.3 | 58 | 26.4 | 88 | 40.2 | 219 | 100 |

The incidence of staphylococcal disease outside the hospital is not well known, but published reports[12,13] indicate that about 5 per cent of the general population manifest staphylococcal infections within one or two years. In comparison, Farrer and MacLeod[14] have reported from the Hospital of the University of Pennsylvania an over-all infection rate of hospital-acquired staphylococcal disease of 13.6 per 1,000 patients (1.4 per cent), or 12.8 per 10,000 patient days. Similarly, in the present report the over-all infection rate was 7.6 per 1,000 patients (0.76 per cent), or 9.5 per 10,000 patient days. These differences may reflect, in part, a more restrictive definition of "infection" by the present authors. To date, these two studies provide the only available data on the frequency of staphylococcal disease in a hospital during a nonepidemic period. The over-all infection rates of 1.4 per cent and 0.76 per cent cannot be construed to indicate a lower infection rate among hospitalized persons as compared to outpatients since the former group has been followed only for the duration of their hospitalization, whereas the populations involved in the outpatient studies[12,13] were observed for one and two years. In comparison, the infection rate among the student nurses in this hospital for 1959 was 13 per cent (26/199).[15]

The factors which determined the monthly variation in the frequency of infections during this investigation cannot be defined. However, it was apparent

that the decline in February was due largely to a decrease in the incidence of postoperative wound infections. Dineen and Pearce[16] have reported a seasonal variation in postoperative wound infections whereas Barnes and his associates[17] did not observe such trends. Despite the apparent seasonal variation in the frequency of wound infections in this hospital in 1959, we have not observed a similar change in 1960.[18] Farrer and MacLeod[14] noted the highest frequency of hospital-acquired staphylococcal infections during the first month of their study, an observation similar to our own. This suggests that such investigations within a hospital may in and of themselves affect the frequency of infection. One can speculate that, with attention being directed to staphylococcal infections, hospital personnel may exercise more stringent control measures.

The present study, as well as the observations of others,[14] illustrates that there are definite variations in the susceptibility of different hospitalized populations to the development of staphylococcal infections. The present problem in this hospital largely concerns postoperative wound infections. For example, the frequency of postoperative wound infections was 13.3 per 1,000 patients, whereas there were 6.7 infections per 1,000 patients on the public medical service and 4.3 per 1,000 patients on the pediatric service. Our findings suggest equal attack rates for persons of different races and both sexes. The attack rates in various age groups show a tendency to increase with increasing age. This may not be a reflection of varying susceptibility with age per se but may reflect the frequency with which certain diseases occur in different age groups. As an illustration, the death rates from cancer, excluding leukemia, show a marked increase with increasing age, reaching a peak of 1,376.8 deaths per 100,000 population in persons 85 and over.[19] Burns resulting from accidents caused by fire, explosions, and hot substances show a frequency of 5.1 per 100,000 population in persons under 10 and a drop to 1.1 per 100,000 in persons 10 to 19. After 19 years of age, however, there is a stepwise increase in the rate which again reaches its peak, with 30.2 per 100,000, in persons 85 and over.[19] Thus, two of the diagnoses most commonly present in patients with postoperative wound infections in our hospital show an increase in the frequency of occurrence with increasing age. Therefore, the increasing rate of infection with increasing age may be a reflection of the frequency with which certain diseases occur in various age groups. In support of this, Barnes and co-workers[17] found no consistent relationship between age and specific infection rates in patients undergoing inguinal herniorrhaphies and abdominal hysterectomies. The frequency of occurrence of epidemics of staphylococcal disease in healthy newborn infants, however, suggests that this age group is highly susceptible to staphylococcal disease. The factors responsible for this susceptibility are not known.

Cancer was present in 18 per cent of the patients who developed staphylococcal infection in the hospital, illustrating the seriousness of the underlying disease. The variation in attack rates in patients with different diagnoses and different types of surgical procedures is apparent and emphasizes the need to specify the type of operation performed, and the patient's underlying diagnosis, for evaluation of surgical sepsis. The attack rates in medical patients are too small to be conclusive but are certainly suggestive that the underlying diagnosis

may be equally important in determining the relative risk of infection. The rate in medical patients with diabetes mellitus in this study, 32 infections per 1,000 patients, is much lower than that observed by others (98.6/1,000).[14] On the other hand, the previous study did not indicate what proportion of the diabetic patients underwent operations.

The higher attack rate of postoperative wound infections on public wards as compared to the private services reported here confirms the findings of others.[14,17] However, one must exercise caution in interpreting this observation as an indication that the environmental differences in these facilities, such as private room versus open wards, are the important factors in determining these rate differences. We have interpreted the present study as well as the data of others[14] to indicate that the underlying diagnoses and types of operations are important factors in determining the frequency of infection. Therefore, it is important to examine the comparability of patients on public and private services as to their diagnoses and types of operation. That the patients are not always comparable is indicated by the data from this hospital for 1957. There were 2,745 discharges from the private surgical service and, of these, 291 patients (10.6 per cent) had cancer, and one (0.04 per cent) had burns. On the public surgical service there were 5,354 discharges; 735 patients (13.7 per cent) had cancer, and 48 (0.89 per cent) had burns. Thus, while the percentage of persons with cancer was roughly the same, there were 22 times as many persons with burns on the public service. Barnes and his associates[17] attempted to minimize these differences by determining the incidence of postoperative sepsis in selected patients who had had abdominal hysterectomies and still found a significantly lower rate of infection on the private service, but the possibility remains that there was a difference in the type or degree of advancement of the underlying diseases in these patients.

The interval between operation and the recognition of sepsis is of considerable practical importance and the finding of a median interval of 7 days suggests that there may be an appreciable number of infections manifested after the patients are discharged from the hospital. The average length of stay for patients on the public surgical service during this study was 10.8 days. Barnes and associates[17] found that some 21 to 32 per cent of instances of wound sepsis, depending upon the type of operation and consequently upon the length of hospital stay, developed after patients were discharged. This factor should be kept in mind when interpreting postoperative wound infection rates and indicates the need for a method for follow-up of discharged patients.

Farrer and MacLeod[14] found a mean interval of 9.8 days and a median interval of 8 days between operation and the recognition of infection and suggested that many operative wounds may become infected on the wards rather than in the operating room. To support this suggestion the authors cited the studies of Elek[20] showing an incubation period of 24 to 48 hours for experimental staphylococcal infection in the skin of man. However, there are certainly factors which may affect the interval between operation and recognition of infection but which were not involved in Elek's studies. Our data indicate, for example, that prophylactic antibiotics may prolong this interval. In fact in Elek's human experiments[21] one of the patients who was inadvertently receiving antibiotics failed

to develop a purulent lesion with an inoculum of four strains of staphylococci, all of which produced pus in another individual. Even in those patients not being given prophylactic antibiotics, however, we found a median interval of 6 days, a great deal longer than the 24 to 48 hours described by Elek. Similarly, Colebeck[13] observed abscess formation within 3 days in an experimentally induced staphylococcal wound infection in a single human volunteer. A second important difference was pointed out by Elek and Conen,[20] who showed that 4 to 8 million staphylococci must be injected into normal human skin to produce infection and suggested that natural infection with such a large dose is improbable and that factors interfering with host resistance must allow the organism to multiply to reach a disease-producing dose. That the incubation period is inversely proportional to the dose or organism has been shown for certain diseases,[22] and it is reasonable to speculate that the same dose-time relationship prevails with the staphylococcus. A naturally occurring staphylococcal infection would therefore be expected to have a longer incubation period than the experimental infections of Elek. Third, the acuity of surgeons in seeking wound infections and the frequency with which wounds are examined are variables seen in the clinical situation but not encountered in the experimental studies. For example, one of the surgical specialities in this hospital does not change any of the dressings on certain types of operations for 7 to 10 days unless the patient has some symptom of wound infection. It is our opinion, therefore, that the experiments of Elek are not comparable to the clinical situation and the 24 to 48 hours between inoculation and the appearance of pus in experimental human skin infection may indeed be considered the "incubation period," whereas the recognition of a postoperative wound infection may not occur for several days after pus develops. Infection may be present in the deeper layers of a wound with a paucity or absence of systemic or local signs, and the infection is *recognized* only when pus makes its way to the surface or some other symptom stimulates probing of the wound. Thus, the interval between operation and the recognition of infection may not correspond with the interval between operation and pus formation. It does not, therefore, seem desirable to utilize the length of this interval as an indication of *where* the infection is acquired.

Duration of hospitalization is a factor of possible importance influencing the frequency of infection in various groups of patients in the hospital. There is no question that patients who acquired infection were hospitalized longer than those who did not, but it is not possible to be certain as to whether or not the patient acquired the infection because he was in the hospital longer, or whether he was in the hospital longer as a result of infection. It should be possible to investigate this factor but could not be done from the data obtained in this study.

The inefficacy of prophylactic antibiotics in preventing postoperative wound infection has been clearly shown.[17,23] Furthermore, the data presented here indicate that prophylactic antibiotics increase the chance of infection resulting from resistant staphylococci.

The staphylococcus can be transmitted by direct or indirect contact and by aerial dissemination,[25,26] but the mode or modes of transmission important in staphylococcal infection are unknown. Colebeck[13] has stated that the staphylo-

cocci present in the environment and exposed to drying are still potential pathogens. Unless one particular route of spread is subsequently shown to be of most importance, it is reasonable to assume that infection may spread by different routes under different circumstances. Thus, there are reports of wound infections attributable to airborne staphylococci[27] and infections secondary to the presence of infected personnel.[7,8] The airborne organisms might be of great significance in producing disease in burned patients whereas such method of spread may be of minimal importance on medical wards. The importance of airborne staphylococci as a source of postoperative wound infections, however, is inconclusive.[32,33] The importance of "autoinfection" has also been discussed.[13,28] In addition, it is possible that the method of spread may vary from ward to ward and hospital to hospital. Gezon and others[29] were unable to determine what routes of spread were most important in a study of an experimentally controlled nursery. Rammelkamp and others[30] have suggested that direct contact of personnel with infants may be the most important method of transmitting staphylococci under normal circumstances in a newborn nursery.

Studies in our nursery[31] have shown that only 5 to 6 per cent of the infants are infected (anterior nares or umbilicus) with colonies of coagulase positive staphylococci before discharge from the hospital; this may explain the low rate of infection in newborn infants. There are persistent carriers of coagulase positive staphyloccocci working in the nursery and the reasons for this low colonization rate are not yet clear. The average length of hospital stay for these infants is 4 days.

The relationship between the length of an operation and wound infection was studied, but no relation was found between the duration of the operation and the development of subsequent staphylococcal infection.

The bacteriophage types of staphylococci producing the hospital-acquired infections were numerous. The 80/81 organism was the most common single typable strain encountered and was responsible for both the epidemics (neurosurgery and nursery) seen during our study. The ability of 80/81 staphylococcus to produce epidemics has been discussed by others.[34] This strain was responsible for only 1/3 of the total number of infections; however, a finding in agreement with that of Farrer and MacLeod,[14] and the problem of hospital-acquired staphylococcal disease is by no means limited to infections with this strain.

## SUMMARY AND CONCLUSION

The incidence of staphylococcal disease in persons hospitalized at The Johns Hopkins Hospital in 1959 is presented. There were 9.5 infections per 10,000 patient days with the highest frequency, 13.3 per 1,000 patients, occurring in postoperative wounds.

The importance of the underlying disease in these patients, predisposing them to infection, is stressed. The highest attack rates were seen among operative patients with burns, cancer, and cholecystitis. The operations with the highest frequency of infection were radical neck dissections, amputations, lobectomies, bone grafts, and cholecystectomies. The need for information about infection

rates in specific populations and in specific types of surgical procedures is emphasized, and an infection rate based on the total number of operations performed may be misleading. On the medical service staphylococcal infection seemed to occur more commonly in patients with systemic lupus erythematosus, dermatitis, diabetes mellitus, and neoplastic disease, indicating further the importance of the underlying disease in predisposition to infection.

The mortality due to staphylococcal infection was 8 and 10 per cent, respectively, on the medical and surgical services.

There was no difference in the attack rates on the basis of race or sex.

The trend toward an increasing attack rate with increasing age probably reflects the frequency distribution of certain diseases among these age groups.

There was a higher attack rate among operative patients on the public service than among operative patients on the private services. There is reason to believe, however, that there are differences in the frequency of certain diseases in these groups, and conclusions cannot be drawn regarding the susceptibility or risk of infection of public versus private patients unless the comparability of the underlying diseases is established.

The interval between operation and the recognition of a wound infection has a median of 6 to 8 days, but this is not acceptable evidence that the infections are not acquired in the operating room.

We were unable to show any relation between the average length of an operation and the frequency with which infection subsequently developed.

Bacteriophage typing of staphylococci revealed that there are numerous strains producing disease in hospitalized patients.

Each hospital must have knowledge of the incidence of staphylococcal disease in its own patients if rational decisions to prevent or control these infections are to be made.

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# Book Reviews

A SYLLABUS OF LABORATORY EXAMINATIONS IN CLINICAL DIAGNOSIS. Critical Evaluation of Laboratory Procedures in the Study of the Patient. Revised Edition. Edited by Lot B. Page, M.D., and Perry J. Culver, M.D. Cambridge, Mass., 1960, Harvard University Press. Pp. 580, indexed. Price $12.50.

This volume is the descendent of *A Syllabus of Laboratory Examinations in Clinical Diagnosis*, edited by Thomas Hale Ham. It is clearly written and the book is at its best when it describes the actual performance of laboratory examinations and their interpretations and limitations. It is at its weakest when it attempts to compress some of the complex physiologic problems into the limited space available. The editors should be especially congratulated in starting out the volume with the two chapters which define "normal" and which provide the necessary caution in evaluation of laboratory data.

Julius R. Krevans, M.D.

DIAGNOSTIC ROENTGENOLOGY OF THE DIGESTIVE TRACT WITHOUT CONTRAST MEDIA. By Bernard S. Wolf, M.D., Mansho T. Khilnani, M. B., and Arthur Lautkin, M.D. New York and London, 1960, Grune & Stratton, Inc. Pp. 180, indexed. $8.75.

In this book, the authors limit their study to the less well-known roentgenologic changes produced by chronic intestinal disease and recorded by films of the abdomen made without the aid of contrast media. The book is divided into four chapters, each being supplemented by characteristic illustrations of good quality. The introductory chapter deals with the radiographic appearance of the normal peritoneal cavity. Points of particular importance which are discussed in some detail include fat tissue delineation of the viscera, gas and fluid distribution within the loops of intestine, the pathophysiology of intestinal gas formation, and the pattern of organic versus functional abnormalities. The subsequent chapters are devoted to lesions of the stomach, the small intestine, and the colon. Here the effect of neoplastic and inflammatory disease upon size, contour, and shape of normal structures is shown and analyzed. A thorough description of the radiographic picture under normal conditions introduces each chapter. Physiologic as well as pathophysiologic data are presented whenever they are helpful for a better understanding of the radiographic findings.

The book is well written and represents an authoritative treatise on the subject. It is concise, yet comprehensive, and the first contribution of its kind in the literature. Gastroenterologists and radiologists in particular will find it an interesting and valuable addition to their library.

Martin W. Donner, M.D.

THE YEAR BOOK OF MEDICINE (1960-1961 Series). Edited by P. B. Beeson, M.D., Carl Muschenheim, M.D., W. B. Castle, M.D., T. R. Harrison, M.D., F. J. Ingelfinger, M.D., and P. K. Bondy, M.D. Chicago, 1960, The Year Book Publishers, Inc. Pp. 740, indexed. Price $8.00.

Each year it becomes more difficult to write a non-fatuous review of this fine annual volume. It occurred to this reviewer that the "numerical method" might prove of some interest, and accordingly certain bits of data were compiled. The smallest differences between the editors obtain in the number of pages and articles contributed or selected. Thus we find a spread of 51 pages between the shortest section and that of Dr. Castle, which is 141 pages in length. Dr. Harrison leads in number of articles abstracted with 104, but he is only 41 articles ahead of the low man in this category. By contrast, the number of editorial comments has a much broader range, with



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Dr. Bondy's lead 71 being almost four times the figure for Dr. Harrison. The length of editorial comments has a similar range, from Dr. Ingelfinger's 18 line average to Dr. Beeson's 4. The total number of lines allocated to editorial comment shows the greatest spread of all, with Dr. Ingelfinger's 823 far outstripping all but Dr. Bondy's 609 and leaving Dr. Harrison's 89 in the dust. It should also perhaps be pointed out that Dr. Muschenheim's section leads in number of graphs, figures, and tables reproduced.

Why these great discrepancies? Are some editors naturally either laconic or garrulous; or is it more a matter of relative effort and application? Can it be that the differences are due to the fields covered—is cardiovascular medicine more clear-cut than gastrointestinal disease? Or duller? It would be interesting to hear responses from the editors on these points; meanwhile I should like again to go on record in favor of the carefully thought out editorial comments—of whatever length—since I suspect that such comments represent for many readers the most valuable part of the *Year Book*.

One might also hope to encourage new sections such as Dr. Ingelfinger's "Liver Title of the Year": "Liver Injury Involving Right Hepatic Artery Ligation, Complicated by Survival."

Louis Lasagna

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HYPERTENSION. Volume VIII, RENAL, ELECTROLYTE AND AUTONOMIC FACTORS. Proceedings of the Council for High Blood Pressure Research, American Heart Association, November, 1959. Edited by Floyd R. Skelton, M.D., Ph.D. New York, 1960, American Heart Association. Pp. 150, not indexed. Price $2.75.

This volume presents the views of six different groups who have been investigating various aspects of blood pressure regulation in normal and hypertensive states.

Most of the material which is contained in this book is available in the published literature, possibly in fragmentary form. This book probably offers the greatest value to the people who are actively engaged in research in this area because the published discussions offer the sentiments of a number of investigators, and their critical analysis of the data is at times quite interesting. This book therefore is a very specialized publication which should serve as a valuable handbook to a smaller number of investigators who are actively interested in this subject.

John H. Laragh

DISEASE AND THE ADVANCEMENT OF BASIC SCIENCE. Edited by Henry K. Beecher. Cambridge, Mass., 1960, Harvard University Press. Pp. 416, indexed. Price $12.50.

For some years now, it has been Dr. Beecher's contention that certain kinds of fundamental advance in science can be made only from study of disease. This new volume records a series of Lowell Lectures organized by Beecher to substantiate his thesis. And impressive indeed is the substantiation. The contributors include such greats as Linus Pauling, Carl Cori, John Enders, William Castle, and René Dubos. The lectures provide a panorama of breathtaking variety, even if an occasional piece seems pompous, long-winded, less than first-rate, or irrelevant to the main theme. Two essays which I found particularly good fun to read were: "The Contribution of Clinical Medicine to Biochemical Genetics" by Alexander Bearn, and "Cardiovascular Physiology: Concepts, and Development of Knowledge" by Nobel Prize winner Dickinson Richards. Highly recommended.

Louis Lasagna

INSULIN. British Medical Bulletin, Vol. 16, No. 3, September, 1960. Published by the Medical Department of the British Council, London. Pp. 261. Price $3.25.

It has been observed on many occasions how fortunate it is that the physician need not understand the mechanism of action of a drug in order to employ it for the therapeutic benefit of his patients. Indeed, it is depressing for the pharmacologist to be asked to list *any* drugs whose basic mechanism of action is well understood. For those pharmacologists who prefer to be miserable

in company, an alliance might be struck up with the endocrinologists, who are none too well off either.

The current issue of the *British Medical Bulletin* documents at some length the extent of our ignorance about insulin, to say nothing of the new surrogates of insulin, the synthetic hypoglycemogens. Yet it also documents the fascinating progress of recent years, and in this way comforts the reader with the vision of a more comprehensive and satisfactory future metabolic Weltanschauung. One cannot but be impressed with the advances in the chemistry of insulin, in insulin assay and insulin antagonists, in the interaction of insulin and fat metabolism, and in the discovery of the sulfonylureas and biguanides. For the clinician solely interested in the immediate pragmatic application of current knowledge in this field, only a few of the essays will be of interest, but for the student or physician seeking a quick review of the area with plenty of references, the issue is, as usual, a bargain.

Louis Lasagna

THE MISREPRESENTATION OF ARTHRITIS DRUGS AND DEVICES IN THE UNITED STATES. A Report to the Committee on Arthritis Advertising, The Arthritis and Rheumatism Foundation. By Ruth Walrad, Research Consultant. New York, 1960, Arthritis and Rheumatism Foundation. Pp. 168, indexed.

This book actually covers a lot more ground than is promised in its title. Over a third of its pages, for example, deal with the development of controls on drug misrepresentation, including such illustrative material from the cancer area as *l'affaire Hoxsey*. Of interest to students of the "hard sell."

Louis Lasagna

THE MODERN TREATMENT OF ASTHMA, WITH SPECIAL REFERENCE TO GOLD THERAPY. By L. Banszky, M.D., L.M.S.S.A. Bristol, England, 1959, John Wright & Sons, Ltd. Pp. 175, indexed. Price $5.00. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents.

This book represents the fruit of almost thirty years of investigation of the use of gold salts in the treatment of bronchial asthma. In 1932, Dudan reported that persistent asthma of many years' standing gradually responded to intravenous injections of gold. Dudan believed in the tuberculous origin of asthma and insisted that gold salts had effect on the asthmatic condition only "if tuberculous origin could be clearly demonstrated by positive Von Pirquet tests." Dr. Banszky, the author of this book, has retained Dudan's belief in the tuberculous origin of asthma, though admitting that in certain cases of asthma the tuberculin skin test may be negative "because we are dealing with an attenuated form of tuberculosis." He advances but does not prove the hypothesis that "certain metabolic changes and influences" secondary to tuberculosis "may affect some part of the adrenocortical mechanism resulting in the condition that we call chronic asthma, in which antigen-antibody reactions are no longer responsible for the development of the asthma attack." He presents the results of gold treatment in over 30 patients. These are uncontrolled but surprisingly impressive, being "good" or "very good" in 64 per cent of one series of 203 patients and in 80 per cent of another series of 100 patients. He suggests that the success of gold may be due to its bactericidal effect on the tubercle bacillus—either a direct in vivo effect which he admits has never been proved, or an indirect effect achieved through stimulation of the organism to "form new substances with bacteriolytic properties."

It is obvious that the opinions presented in this book are hard to reconcile with the following well-established facts on asthma: (1) Evidence of tuberculosis can almost never be found in asthmatic American children. (2) No adrenocortical deficiency has been demonstrated in asthma. (3) Gold has not been shown to be useful in the chemotherapy of tuberculosis.

Notwithstanding, the reported results of gold treatment for asthma are sufficiently impressive to warrant confirmation (or refutation) by a controlled study and to recommend this book to students of the disease.

Thomas E. Van Metre, Jr.

HUMAN PITUITARY HORMONES. Ciba Foundation Colloquia on Endocrinology, Vol. 13. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. Boston, 1960, Little, Brown & Company. Pp. 336, indexed. Price $9.50.

A symposium on the anterior pituitary hormones was held on Aug. 6 to 8, 1959, to honor Professor B. A. Houssay. This volume reports the papers and discussions given at that time.

Fraser opened the scientific discussion with a review of the anatomy of the pituitary fossa and the use of radioisotopes for ablation of the gland. Wilhelmi discussed the fractionation of human pituitary hormones, and methods for assaying these materials, and gave estimates of the amount of each trophic hormone contained in the normal pituitary gland. Li reviewed extensive immunochemical studies on human pituitary growth hormone. Follicle-stimulating hormone and human interstitial-cell-stimulating hormone were isolated and studied in highly purified form. Read and Bryan described an immunoassay for growth hormone that appears to have sufficient specificity, sensitivity, and reliability to be considered a major endocrine advance. Raben and Hollenberg have discussed the effect of growth hormone on the mobilization of fatty acids. The mechanism by which the growth hormone augments the release of fatty acid from adipose tissue is re-examined. Evidence is developed to demonstrate that both glucose and insulin inhibit the release of fatty acid from adipose tissue. This appears to be related to inhibition of the esterification of the fatty acids. Ikkos and Luft contrasted the difference in the metabolic effects of growth hormone in diabetics with and without intact pituitary glands. In the discussion that followed many of the current concepts of the action of growth hormone were re-examined. Fraser and Harrison presented the experimental work on the effects of growth hormone on urinary calcium excretion. Increased excretion of calcium and radioactive strontium was observed in hypophysectomized animals only if the parathyroid gland was present. Hypercalciuria with normal serum calcium was also seen following administration of growth hormone to hypophysectomized human subjects. Beck and co-workers illustrated the physiologic responses of human subjects to growth hormone with extensive balance studies. Venning and his associates showed that growth hormone caused a rise in the level of urinary aldosterone. The volume concluded with reports on the gonadotropins, melanocyte-stimulating hormone, and thyrotropic hormone. A general review by the participants summarized the conference.

This is a collection of reports and discussions on human pituitary hormones that is unprecedented in current publications. Investigators, as well as those engaged primarily in clinical endocrinology, will be equally rewarded by these contributions.

Thaddeus E. Prout

THE LIVER AND CANCER: A NEW CANCER THEORY. By Kasper Blond, M.D., F.R.C.S., with a foreword by E. Stanley Lee, M.S., F.R.C.S. Second Edition. Bristol, England, 1960, John Wright & Sons, Ltd. Pp. 400, indexed. Price $8.00. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents.

Why do reputable publishing houses put out books like this one? The author has a theory—that cancer is due to a sick liver—but that's about all. Unlike Peller's *Cancer in Man*, at which Blond blasts away with some frequency, *The Liver and Cancer* is quite obviously *not* a scholarly compilation of interesting and useful information, but rather a disjointed and unconvincing bit of "hobbyhorse riding." It is hard to understand how Blond's opus got into print in the first place, but a *second* edition seems sheer cussedness.

Louis Lasagna

# Announcements

The University of Colorado School of Medicine announces the COCHEMS COMPETITION, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of "The Diagnosis, Etiology, and Treatment of Thrombophlebitis." The competition is open to all physicians, and entries must be received, in triplicate, on or before Oct. 1, 1961.

The Colorado National Bank of Denver, trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges, appointed by him, are Dr. Michael E. De Bakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time, the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation, "Awarded the Jane Nugent Cochems Prize."

Further questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice-President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.

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THE 38TH ANNUAL CONFERENCE OF THE AMERICAN PHYSICAL THERAPY ASSOCIATION will be held at The Palmer House in Chicago, Illinois, on July 2 to 7, 1961.

The theme of the scientific program will be "Aftercare Programs," dealing specifically with the pediatric patient, the ambulatory adult, and the geriatric patient.

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A two-week course in REHABILITATION OF THE CHRONICALLY ILL PATIENT will be held April 24 to May 5, 1961, at the Bird S. Coler Hospital, Welfare Island, New York City, conducted by the Department of Physical Medicine and Rehabilitation, New York Medical College–Metropolitan Medical Center.

Intended for registered nurses, occupational therapists, physical therapists, and social workers, the course will consist of lectures, seminars, clinical demonstrations, and practical workshops and will include the contributions of the various disciplines to the rehabilitation process.

The curriculum is as follows:

Public Health Aspects
Community Needs and Resources
Home Care Programming
Sheltered Workshop
Prosthetic Devices
Physiology and Pathology
Psychological and Social Aspects
Nutrition and Dental Care
Clinical Conditions
Interdisciplinary Cooperation
Self Care Activities
Evaluation and Management:
The Bedridden Patient and
Incontinent Patient
The Ambulatory Patient
The Patient in the Community

The course is supported by the United States Office of Vocational Rehabilitation. A number of Federal scholarships may be available for tuition, maintenance, and travel.

For further information and application forms, write to Raymond C. Lerner, M.S.S.W., Coordinator, PostGraduate Education, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York 29, N.Y.